Uniwersytet im. Adama Mickiewicza

Wydział Chemii

Organic chemistry in laboratory

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UAM

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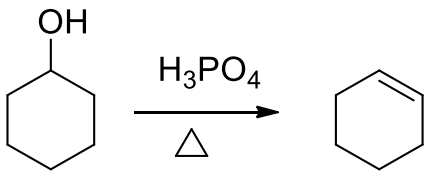
1. CYCLOHEXENE



Reagents:

cyclohexanol	5 g; 5.19 mL
H_3PO_4 85%	1.5 mL

Instrumentation and glassware:

two-necked round-bottom flask 25 mL
dropping funnel
fractioning column
thermometer
condenser
receiving flask
stirrer-heat plate
oil-bath
cooling bath

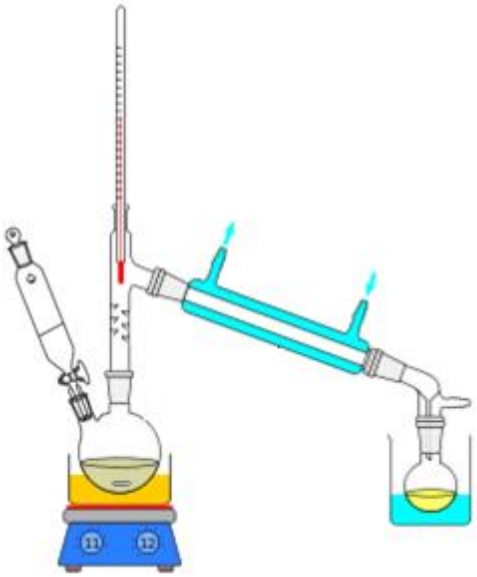


Figure 1. Dehydratation of cyclohexanol

Note: The reaction apparatus should be set up (**Fig**. **1**), so that the dropped cyclohexanol does not run down the hot walls of the two-necked round-bottom flask, as it may break. It is preferable to use a flask with straight necks or place a dropper in the middle neck of the flask.

Fit a 25 mL two-necked round-bottom flask with stirring bar, a dropping funnel and with fractioning column with condenser carrying a thermometer at its upper end. A receiving flask place in an ice-bath to minimize cyclohexene evaporation during distillation.

Place 1.5 mL of 85% H_3PO_4 in the two-necked round-bottom flask, and heat it in an oil bath at 160–170 ^oC. Fill the dropping funnel with cyclohexanol (5 g; 5.16 mL), and add it slowly (over a period of 20 min) to the flask with the acid.

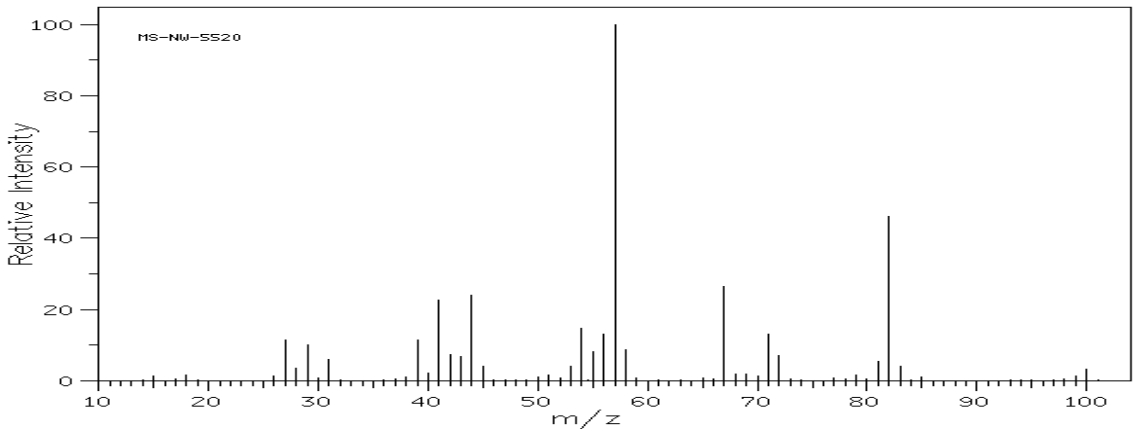
When all cyclohexanol is introduced, raise the temperature of the oil bath to about 200 °C and maintain it at this temperature for 20 minutes, and start the distillation. The temperature at the top of the column should not rise above 100 °C.

Cyclohexene fractions are collected in the range of 80–90 °C.

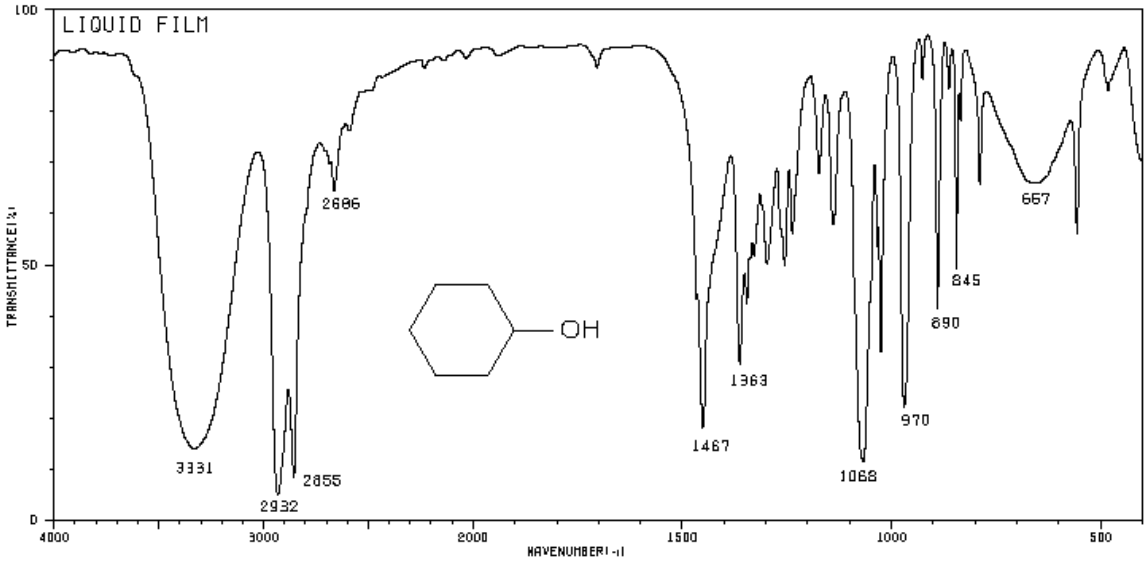
The collected distillate is saturated with NaCl, and the solution is decanted from the NaCl into a separatory funnel, and alkalize with 10% Na_2CO_3. Separate the upper layer and dry the organic layer over anhydrous Na_2SO_4. The yield of cyclohexene is 80%.

SPECTRA

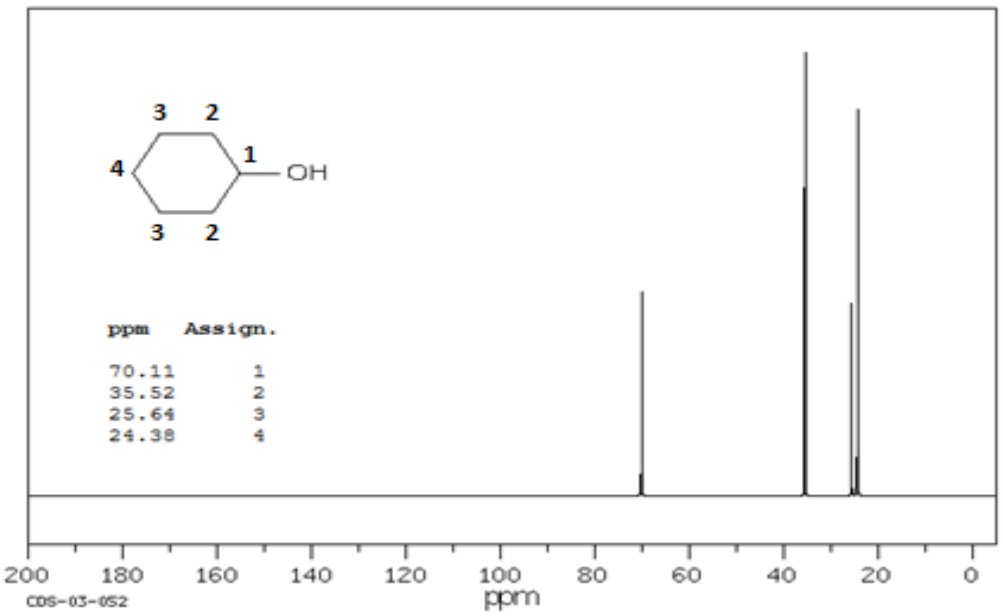
a) Mass spectrum of cyclohexanol



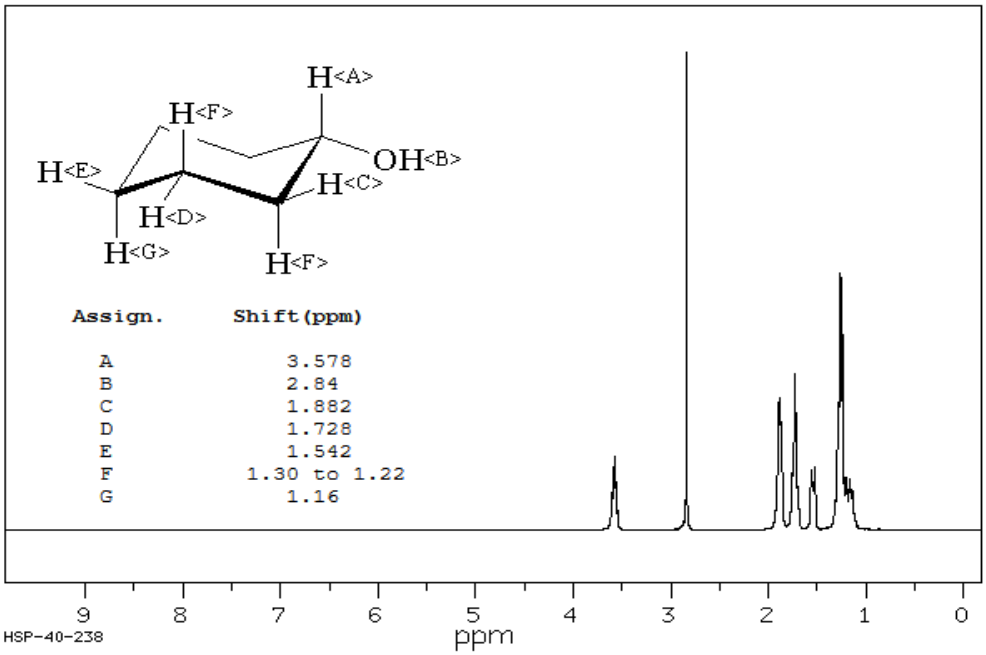
b) FT-IR spectrum of cyclohexanol (liquid)



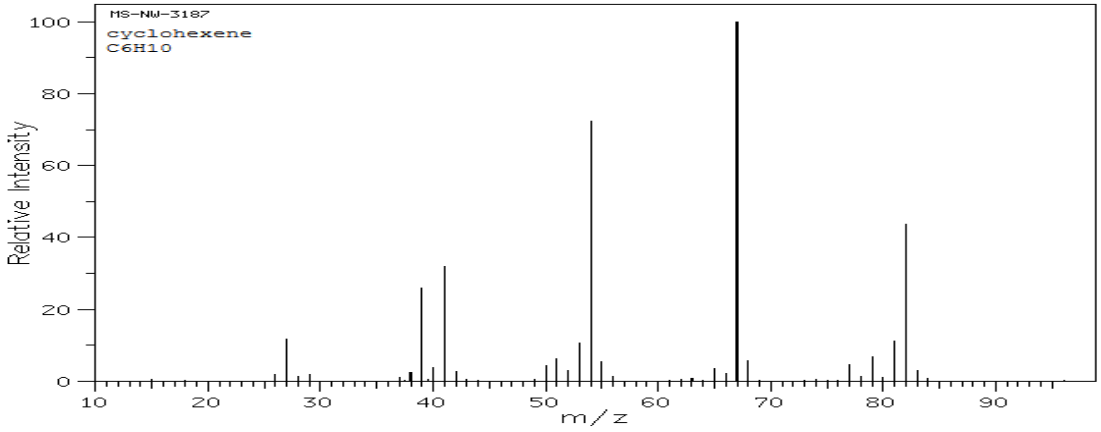
c) ^{13}C NMR spectrum of cyclohexanol in chloroform-*d*



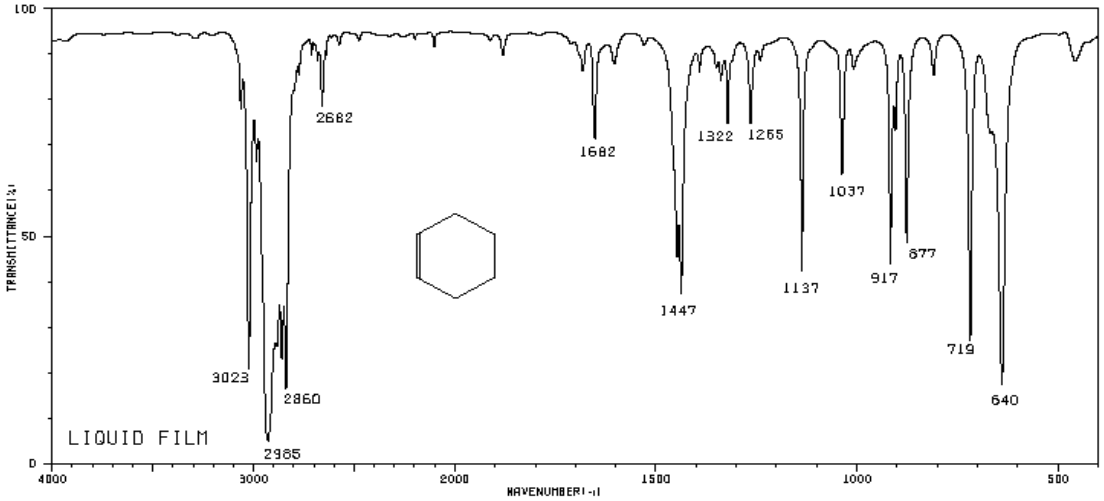
d) ^{1}H NMR spectrum of cyclohexanol in chloroform-*d*



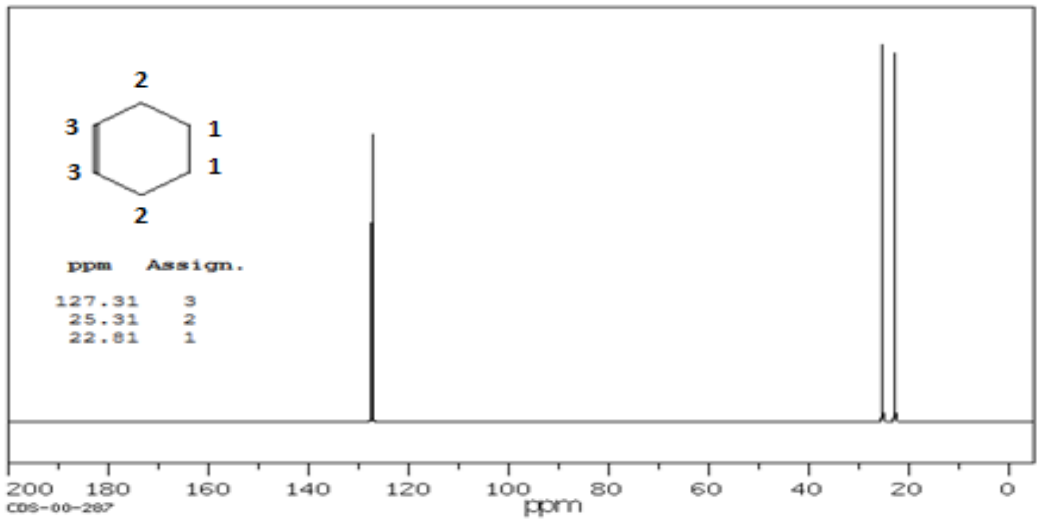
e) Mass spectrum of cyclohexene



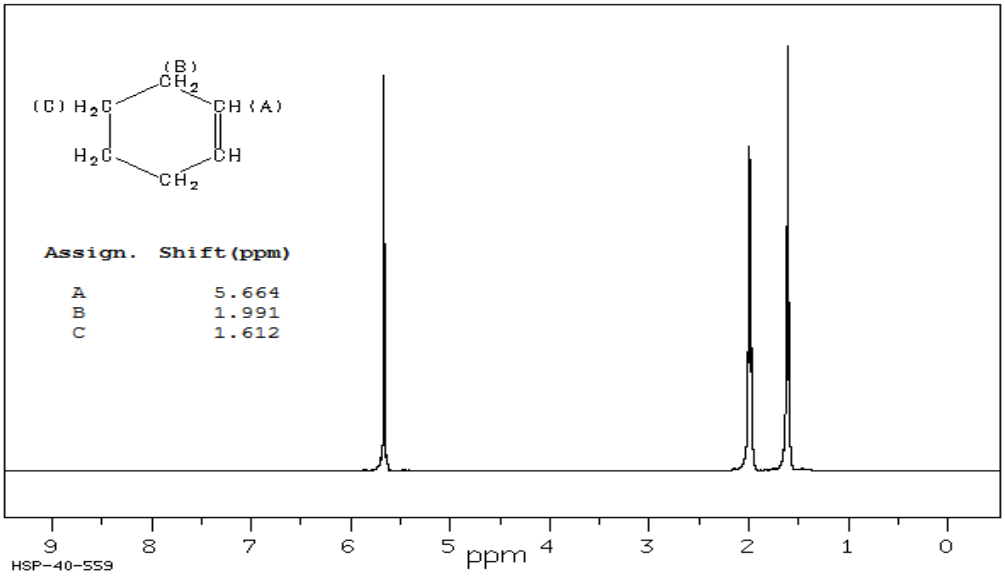
f) FT-IR spectrum of cyclohexene (liquid)



g) ^{13}C NMR spectrum of cyclohexene in chloroform-*d*

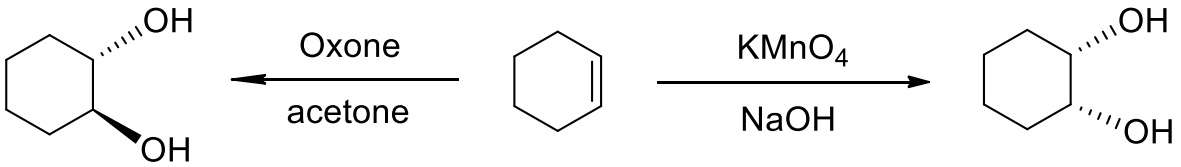


h) ^{1}H NMR spectrum of cyclohexene in chloroform-*d*



2. *CIS*- AND *TRANS*-1,2-DIHYDROXYCYCLOHEXANE

(small scale and scale-up the syntheses)



Reagents:

cyclohexane	50μL (x2) + 15 mL
Oxone®	0.4 g + 4 g
acetone	2 mL + 10 mL
conc. HCl	0.1 mL + 1 mL
$KMnO_4$	100 mg + 1 g
tert-BuOH	2 mL + 10 mL
0.1 M NaOH	4 mL + 40 mL
p-anisaldehyde	14 mL
conc. H_2SO_4	18 mL
98% ethanol	500 mL

Instrumentation and glassware:

round-bottom flasks 5 mL
round-bottom flasks 50 mL
vials
crystallizers
magnetic stirrers
separatory funnel
filtering flask with Büchner funnel
glass funnel

SAFETY:

Oxone® solution is strongly oxidizing and should not come into contact with skin.

Reaction 1. Oxone reaction (A-1)

Dissolve 0.4 g Oxone® in 2.0 mL of water in a sealed vial.

Dissolve 50 μL of cyclohexene in 2.0 mL of acetone in a small round-bottom flask. Cool down the cyclohexene solution in an ice bath, then add the Oxone® solution dropwise over 5 minutes with swirling in the ice bath.

Remove the flask from the ice bath and allow the reaction to sit for 15–30 minutes, then add 0.1 mL of conc. HCl to the reaction dropwise with swirling. Allow the reaction to sit for about 10 minutes.

Reaction 2. $KMnO_4$ reaction (B-1)

Dissolve 100 mg of $KMnO_4$ in 4.0 mL of 0.1 M NaOH solution in a small round-bottom flask and cool in an ice bath.

Dissolve 50 μL of cyclohexene in 2.0 mL of *tert*-butanol in a vial and quickly add into the $KMnO_4$. Swirl the flask in the ice bath for 3–5 minutes, then remove the flask from the ice bath and allow to sit for 10 minutes.

Thin Layer Chromatography (TLC):

On a TLC plate mark 3 spots: A-1/co-spot/B-1 and spot each mark with the appropriate solution. For the most successful plate, be sure to spot each sample lightly. It may be hard to spot the $KMnO_4$ slurry, but keep trying. Use a hair-dryer to dry the aqueous spots.

Develop the plate in a chamber with ethyl acetate as the eluent. Remove it from the chamber and mark the solvent front.

Take the plate and gently stain it by dipping into *p*-anisaldehyde solution (**C**). Then, remove excess of stain with a paper towel, and heat the plate on a hot plate until the spots develop.

Spot TLC lightly. The compounds show up well by stain, so heavy spotting is unnecessary and can lead to smearing. If spotted lightly, the *cis* isomer staining red/purple at a R_f value of 0.37 and the *trans* isomer staining blue at a R_f value of 0.31.

The *p*-anisaldehyde stain (**C**): mix 500 mL of 95% ethanol with 18 mL of conc. H_2SO_4, and 6 mL of glacial acetic acid. The solution is then warmed, and 14 mL of *p*-anisaldehyde is added with stirring.

The anisaldehyde staining solution is light-sensitive and should be stored in the refrigerator.

Observations and Results:

In your laboratory notebook, include observations of the experiment you performed. Draw a picture of your TLC plate to scale and describe it accurately. Include distances necessary for determining R_f values. Add information about your developing solvent and stain.

SCALE-UP – STEP 2:

Oxone reaction (A-2)

In round-bottom flask with stirring bar, dissolve Oxone® 4.0 g in 20 mL of water. Cover the flask with septum and stir a solution using a stirrer. Oxone® solution is strongly oxidizing and should not come into contact with skin.

Dissolve 5 mL of cyclohexene in 10 mL of acetone in a small Erlenmeyer flask. Cool the cyclohexene solution in an ice bath, then add the Oxone® solution dropwise over 5 minutes with swirling in the ice bath. Remove the Erlenmeyer flask from the ice bath and allow the reaction to sit. After 15–30 minutes, start to stir on the magnetic stirrer and add slowly 1 mL of conc. HCl to the reaction mixture. Then allow the reaction to sit for about 10 minutes. Then, remove on Büchner funnel the inorganic sediment and concentrate the organic layer on rotary evaporator. Weight it. Then add silica gel to the oil and evaporate to dryness.

Concentrate the organic solution using a rotary evaporator. Add silica gel to the oil and evaporate to dryness.

Column preparation

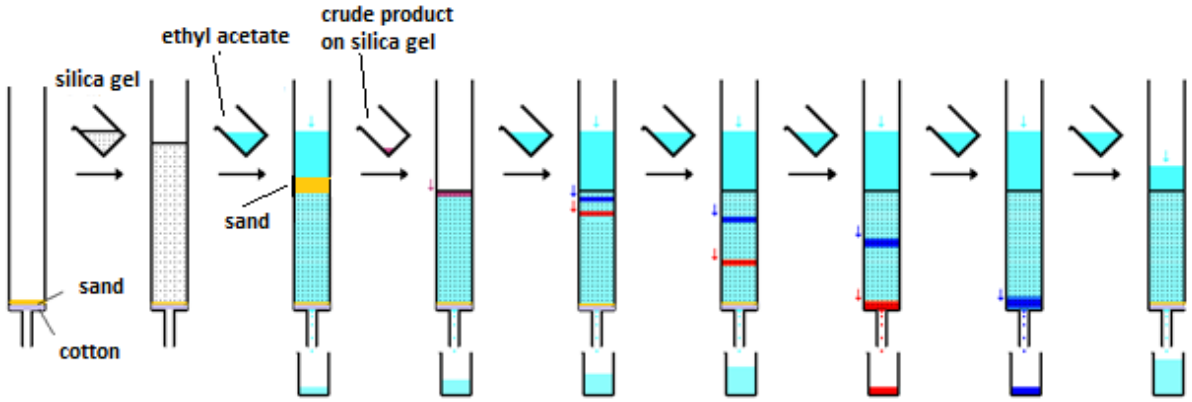


Figure 2. Column preparation.

Prepare the chromatography column (**Fig**. **2**). Ask the teacher for help.

Plug the column with a small amount of cotton and set it up on the stand. After setting on the stand, close the valve of the column. Then, add some sand and pour gently the slurry of silica gel in ethyl acetate up to the top of the column. Open the tap of column and allowed the silica gel to pack. In case of bubble formation in your column, slap the column gently with the rubber tube to remove the bubbles of air. Pour the additionally portion of ethyl acetate to pack property the column.

When the column is packed with 0.2 cm of solvent layer above the bed, close the valve.

Remember: Never let the column run dry at any point, as this will lead to infiltration of air and rapid cracking of the column.

Flatter gently the surface (the top bed) with flattened glass rode, sprinkle some sand to cover the top and allow for better protection. After it, gently load your sample to the top bed the of silica gel. Then, wash the glass column walls with eluent using a disposal pipette. Use small amount of ethyl acetate as the eluent just to be sure that your sample get to the silica gel below the sand in the column. Ensure that all your loaded sample enters the column before refilling the column with eluent. Then, gently add the rest of the eluent.

Open the tap of the column, and collect the fractions into the numbered vials.

The product is waxy solid, m.p. 105−107 ºC.

$KMnO_4$ reaction (B-2)

Dissolve 1.0 g of $KMnO_4$ in 40 mL of 0.1 M NaOH solution in a round-bottom flask. Cool the $KMnO_4$ solution in an ice bath. Then, dissolve 5.0 mL of cyclohexene in 10 mL of *tert*-butanol in a small Erlenmeyer flask. Quickly add the cyclohexene solution into the $KMnO_4$. Stir the flask in the ice bath for 3–5 minutes. Remove the reaction mixture from the ice bath, and allow to sit for 15 minutes. Then, remove from the flask the stirring bar. Add dichloromethane and transfer the mixture to a separatory funnel. Separate the organic layer from water fraction. Water extract 3 x 20 mL. Combine together the organic fractions, dry with anh. K_2CO_3 (ca. 30 min) then filtrate through the glass funnel with cotton plug. Wash the drying agent on funnel with DCM. Transfer the dry solution into clean, dry and weighted round-bottom flask and concentrate it on rotary evaporator. Take under consideration very high boiling points of the solvents (*tert*-butanol). Weight it. Then add silica gel to the oil and evaporate to dryness.

Prepare the preparative column and purify the crude product (waxy solid, m.p. 98−99ºC).

The glassware is stained brown in the permanganate reaction. It is manganese dioxide that can be removed by soaking in a warm solution of citric acid or with diluted HNO_3 solution.

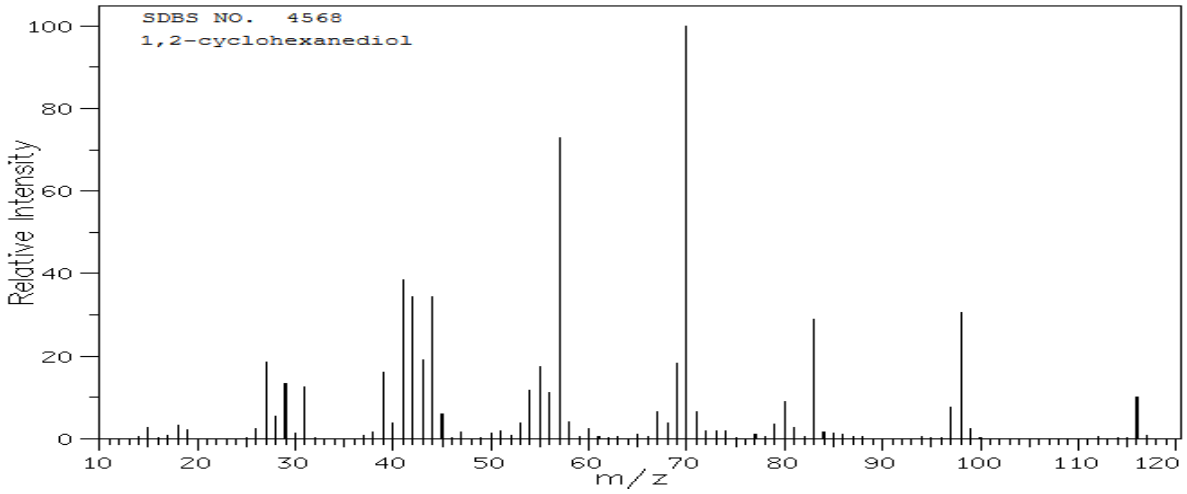
The isolated products characterize by IR, melting point, and TLC.

Check if the products of the experiment matched the characterization of authentic *trans*-cyclohexane-1,2-diol and *cis*-cyclohexane-1,2-diol.

SPECTRA

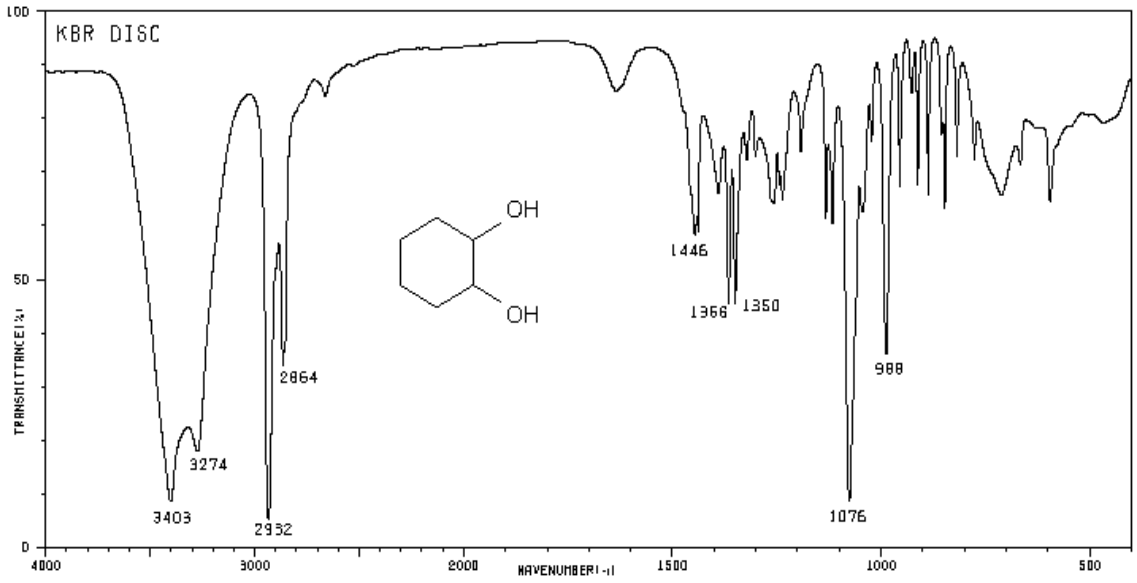
The **spectral analysis of cyclohexene** is presented in chapter 1.

a) Mass spectrum of cyclohexane-1,2-diol.



MS (EI, 70 eV) m/z 116 (M+, 12), 98 (38), 83 (37), 70 (100), 57 (53).

b) FT-IR (KBr) spectrum of cyclohexane-1,2-diol – mix of isomers.



Spectra data of isomers:

trans-cyclohexane-1,2-diol waxy solid, m.p. 105−107 °C.

^{1}H NMR (D_2O, 400 MHz) δ: 3.27 (br s), 1.83 (br s, 1H), 1.58 (br s, 1H), 1.16 (br s, 1H).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.06 (br s, 2H), 3.48 (m, 2H), 2.15 (m, 2H), 1.89 (m, 2H), 1.48 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 84.1, 34.3, 25.5.

IR (KBr): 3380, 1445, 1360, 1350, 1290, 1235, 1195, 1065, 1040 cm^{-1}.

cis-cyclohexane-1,2-diol waxy solid, m.p. 98−99 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.00 (br s, 2H), 3.88 (m, 2H), 1.95 (m, 2H), 1.78 (m, 4H), 1.51 (m, 2H).

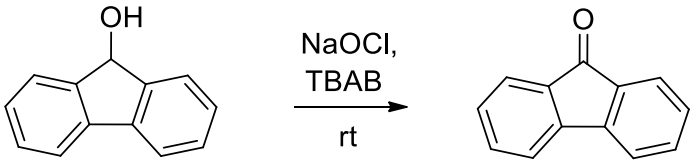
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 72.0, 31.1, 23.0.

IR (KBr): 3395, 3275, 2516, 2430, 1440, 1365, 1260, 1130, 1075 cm^{-1}.

References

Burlingham B. T., Rettig J. C.: Evaluating Mechanisms of Dihydroxylation by Thin-Layer Chromatography. A Microscale Experiment for Organic Chemistry. *J. Chem. Educ*. *85*(7) **2008**, 959–961.

3. 9-FLUORENONE



Reagents:

fluorenol	1.0 g (d=1.15 g/mL)
NaOCl	15 mL
TBAB	0.3 g

Instrumentation and glassware:

round-bottom flask 100 mL
stirring bar
separatory funnel 100 mL
filtering flask with Büchner funnel

In a 100 mL round-bottom flask, 1.0 g of fluorenol, 30 mL of ethyl acetate and a stirring bar are placed. Next, NaOCl (15 mL) and TBAB (0.3 g) as a catalyst are added to the vigorously stirred solution. Usually, oxidation is completed after 60 minutes. After completion of the reaction (TLC control), the phases are separated and the aqueous layer is extracted with 20 mL of ethyl acetate. The combined organic layers are washed with water and dried with anhydrous $MgSO_4$. After filtration, the solvent is evaporated to dryness under reduced pressure. The crude reaction product is crystallized from *n*-hexane to form yellow crystals (lit. m.p. = 82–84 ^oC). The crystals are filtered and dried on air.

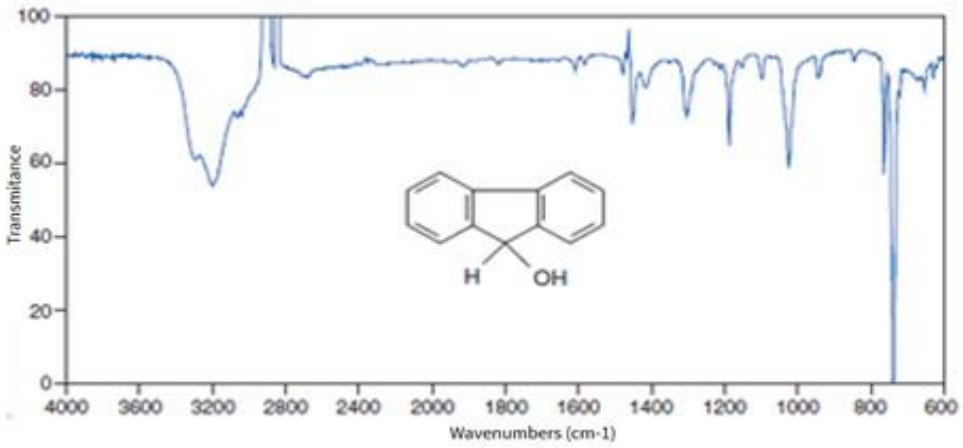
Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate).

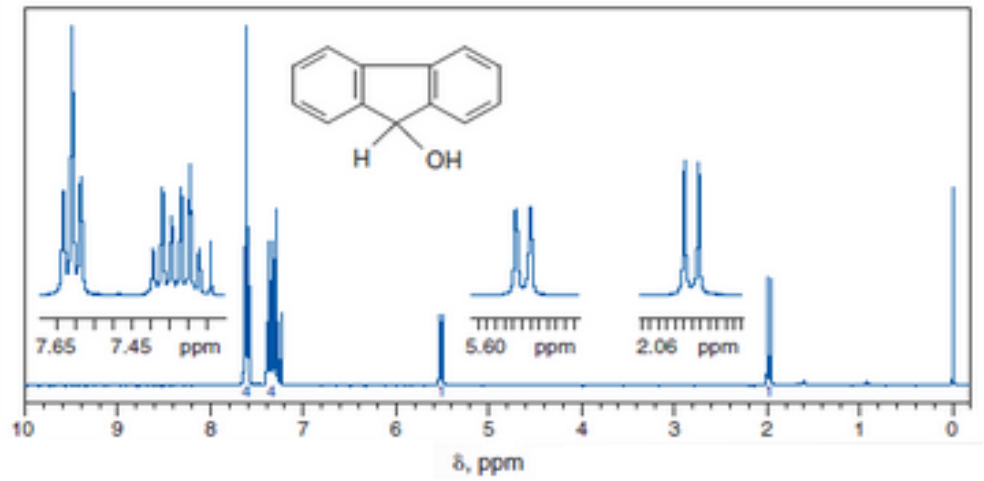
Develop with *n*-hexane/ethyl acetate (8:2). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

SPECTRA

a) FT-IR spectrum of 9-fluorenol in KBr disc.

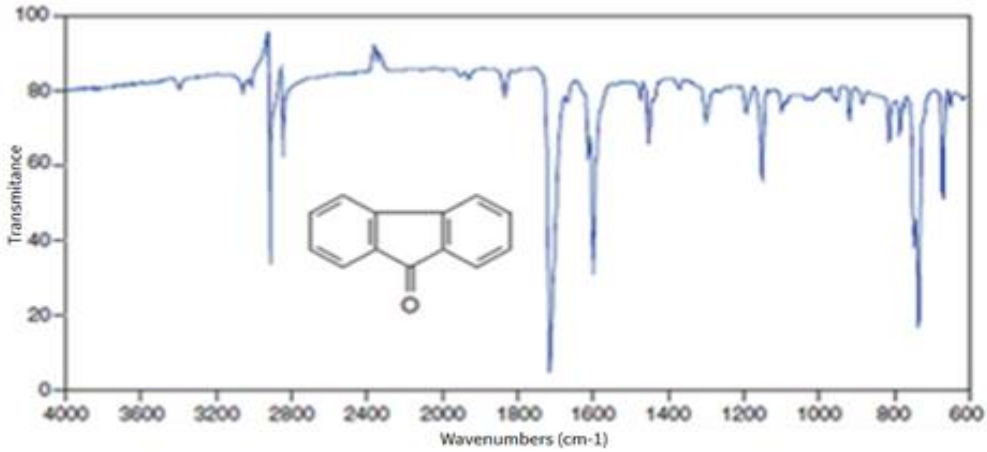


b) ^{1}H NMR spectrum of 9-fluorenol in chloroform-*d*

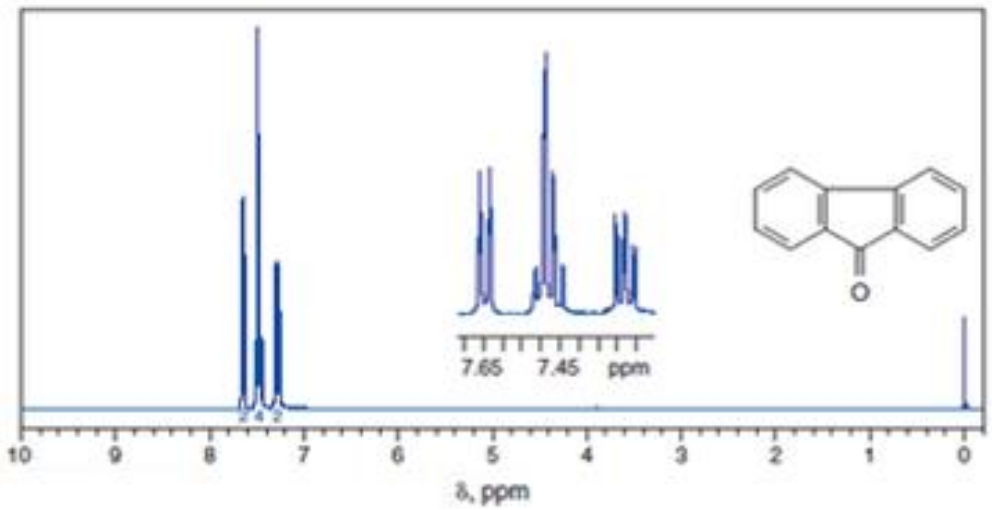


c) **^{13}C NMR** data of 9-fluorenol in in chloroform-*d* ; δ: 73.8, 119.6, 125.0, 127.2, 128.2, 139.5, 146.8

d) FT-IR spectrum of 9-fluorenone in KBr disc.

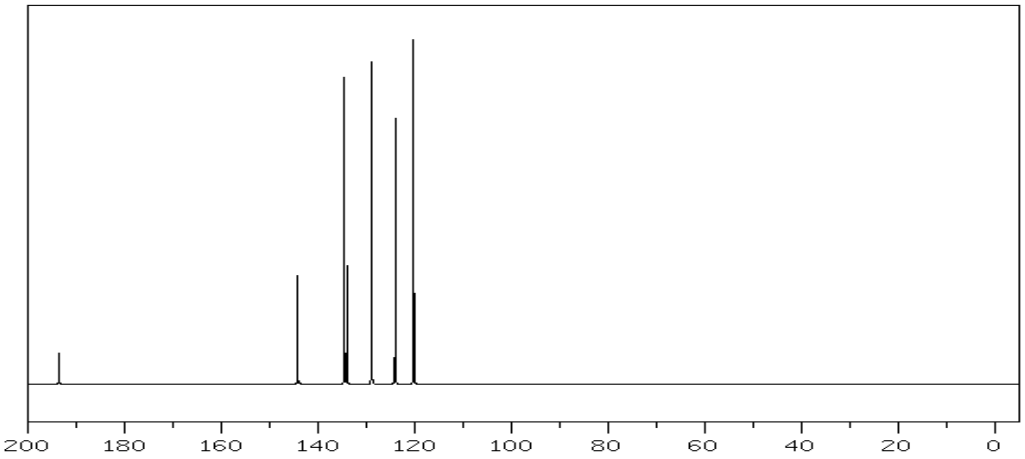


e) ^{1}H NMR spectrum of 9-fluorenone in chloroform-*d*



f) ^{13}C NMR data of 9-fluorenone in chloroform-*d;*

δ: 120.1, 123.8, 128.8, 133.9, 134.4, 144.1, 193.1 ppm.



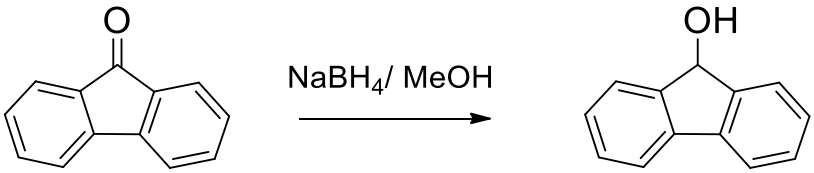
References

Pavia, D. L.; Lampman, G. M.; Kritz, G. S.; Engel, R. G. *Introduction to Laboratory Techniques*, 4th Ed. Thomson Brooks/Cole: Mason, OH, 2006; pp 46-50.

https://open.bu.edu/handle/2144/1494

https://www.chegg.com/homework-help/consider-spectral-data-9-fluorenol-figs-1713-1714-function-chapter-17.4-problem-14e-solution-9781439049143-exc

4. 9-FLUORENOL



Reagents:

fluorenone	0.4 g
$NaBH_4$	0.1 g
methanol	400 mL
CH_2Cl_2	
water	

Instrumentation and glassware:

25 mL round-bottom flask
beakers (25 and 50 mL)
graduated cylinder
Büchner funnel with vacuum flask
Pasteur pipets
capillary tubes for TLC
TLC plate

Thin layer chromatography (TLC):

Before you set up your reaction, obtain a large TLC plate and 4–5 capillary tubes, which you will use to monitor your reaction for a total of 2 minutes (0 s, 15 s, 30 s, 60 s, 90 s, 120 s). On the plate, put also a reference spot for fluorenone (dissolve in CH_2Cl_2 and test the concentration of your solution by TLC under UV lamp before running the reaction). The developing solvent is 100% dichloromethane.

Make sure this TLC plate is prepared prior to setting up the reaction. Once you have the plate set up, you can the reaction.

In a 25 mL round-bottom flask, add 0.4 g fluorenone and dissolve it in 8 mL methanol. Add a stir bar, and stir the mixture at room temperature (do not cap the flask – H_2 will evolve during the reaction).

On your TLC plate, spot your sample of fluorenone (this is the reference), then spot your reaction mixture with a different capillary tube (this is t = 0 s). Obtain 100 mg (0.1 g) of $NaBH_4$ – work quickly, as $NaBH_4$ absorbs water from the atmosphere. Add the $NaBH_4$ to the reaction mixture in approximately 5 equal portions at the times indicated (begin recording the time after the first portion has been added). At the same time, take an aliquot of your reaction mixture with a capillary tube, and make a spot on your TLC plate in the appropriate position.

Monitor the reaction for a total of 2 minutes, at which point you can develop your TLC plate. If your reaction is complete, to reaction mixture add 2 mL of water and heat the mixture to a boil or until all of the solid has gone into solution. Then, remove the flask from the heat, and let it slowly cool to room temperature. Collect your product crystals by vacuum filtration on a Büchner funnel with a filter disc. Wash the crystals with 4:1 (v/v) MeOH : H_2O (3 x 1 mL), and then transfer to a tared beaker. Dry on air for a few minutes to remove excess of water.
Calculate the yield, check melting point (lit. 152-155^oC) and measure the IR spectrum of both fluorenone and fluorenol. Compare the obtained data.

Thin layer chromatography (TLC):
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate).
Develop with *n*-hexane/ethyl acetate (8:2). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

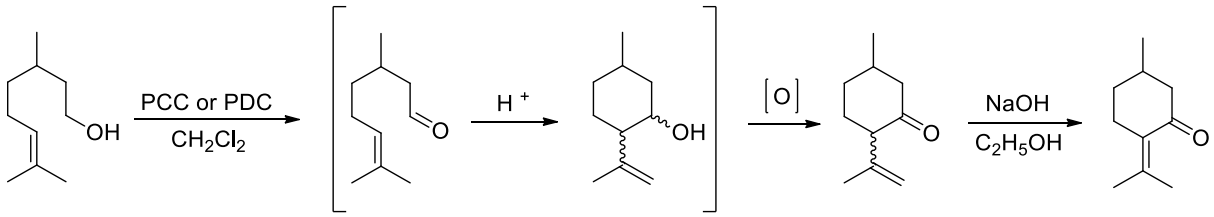
SPECTRA

The **spectral analysis of 9-fluorenol** is presented in chapter 3 (synthesis of 9-fluorenone).

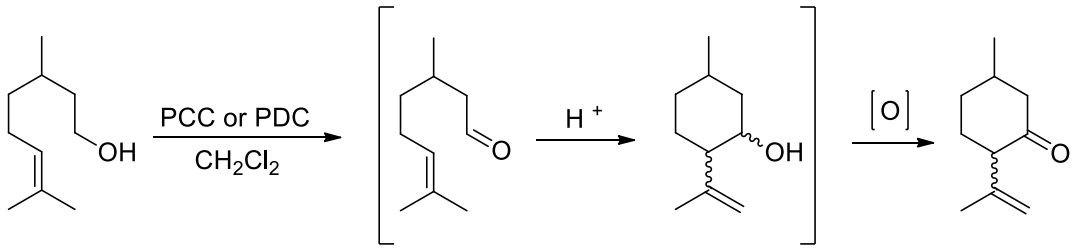
References

Pavia, D. L.; Lampman, G. M.; Kritz, G. S.; Engel, R. G. *Introduction to Laboratory Techniques*, 4th Ed. Thomson Brooks/Cole: Mason, OH, 2006; pp 46-50.
https://open.bu.edu/handle/2144/1494
https://www.chegg.com/homework-help/consider-spectral-data-9-fluorenol-figs-1713-1714-function-chapter-17.4-problem-14e-solution-9781439049143-exc

5. PULEGONE (2-step synthesis)



STEP 1 ISOPULEGONE – "ONE POT" REACTION



Citronellol (racemic form)	citronellal	isopulegol 4 isomers	isopulegone 2 isomers

Reagents:

citronellol	1.0 g
PCC	4.0 g
dry CH_2Cl_2	25 mL
Celite	
anh. K_2CO_3	

Instrumentation and glassware:

round-bottom flask 50 mL
magnetic stirrer
separatory funnel
filtering flask with Büchner funnel
glass funnel

To a suspension of 4.0 g of PCC (or PDC) in 25 mL of dry CH_2Cl_2, add 1.0 g of citronellol. The slurry has to be stirred at room temperature for 36 hours or just leave it without stirring for one week. From time to time the flask with the mixture should be shaken till its content is mixed. Monitor the reaction with TLC (the mobile phase: CH_2Cl_2). When the reaction is completed, filter the mixture through Celite and the solids wash thoroughly with CH_2Cl_2.

Isolation and purification. Then, acidify the mixture with 10% HCl (necessary reduction of the carcinogenic Cr(VI) compounds to non-toxic Cr(III) salts), and move to separatory funnel. Separate the fractions and wash the organic one with 10% $NaHCO_3$, and next with water

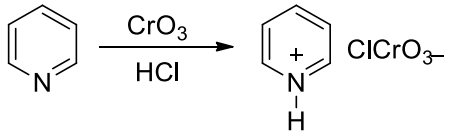
(3 x 20 mL). Dry organic fraction with anhydrous K_2CO_3 and concentrate it on the rotary evaporator to remove CH_2Cl_2.

Weight the obtained crude yellow oil, calculate the percentage yield and characterize by TLC, IR and GC-MS. The crude product can be used to the second step of reaction.

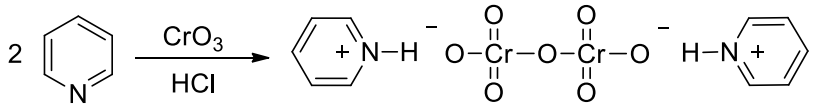
Thin layer chromatography (TLC):

Develop SiO_2 plate in *n*-hexane/ethyl acetate (9.5:0.5, v/v), then mark the spots with pencil under UV light.

The oxidation of alcohols by PCC (pyridinium chlorochromate) or **PDC** (pyridinium dichromate) works under mild conditions and can be used for compounds containing unstable functional groups. This method is useful to synthesize aldehydes, whereas the Jones and the Sarett-Collins oxidations are better suited to the synthesis of ketones. PCC is acidic, therefore can react with unstable functional groups. On the other hand, PDC is closer to neutral. In DMF, the reaction of primary alcohols with PDC (except for allyl alcohols) leads to complete oxidation to carboxylic acids.



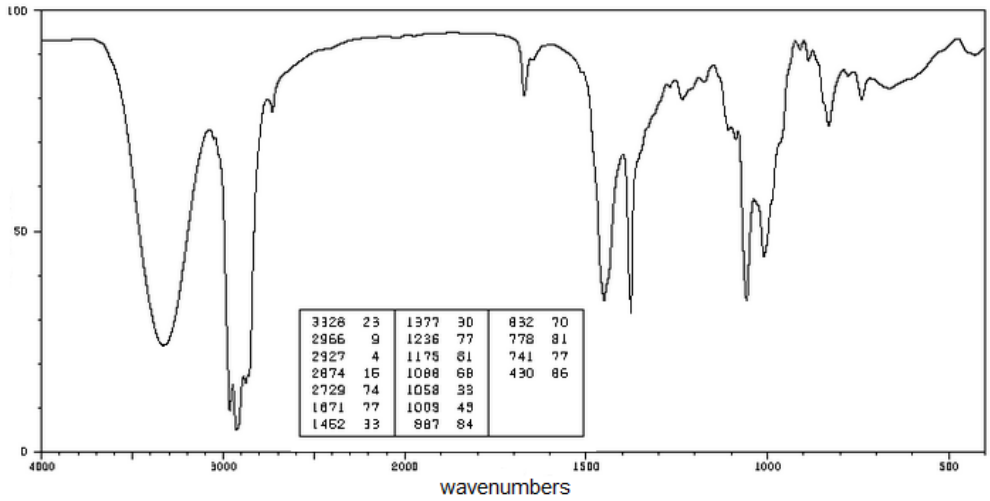
PCC - pyridinium chlorochromate



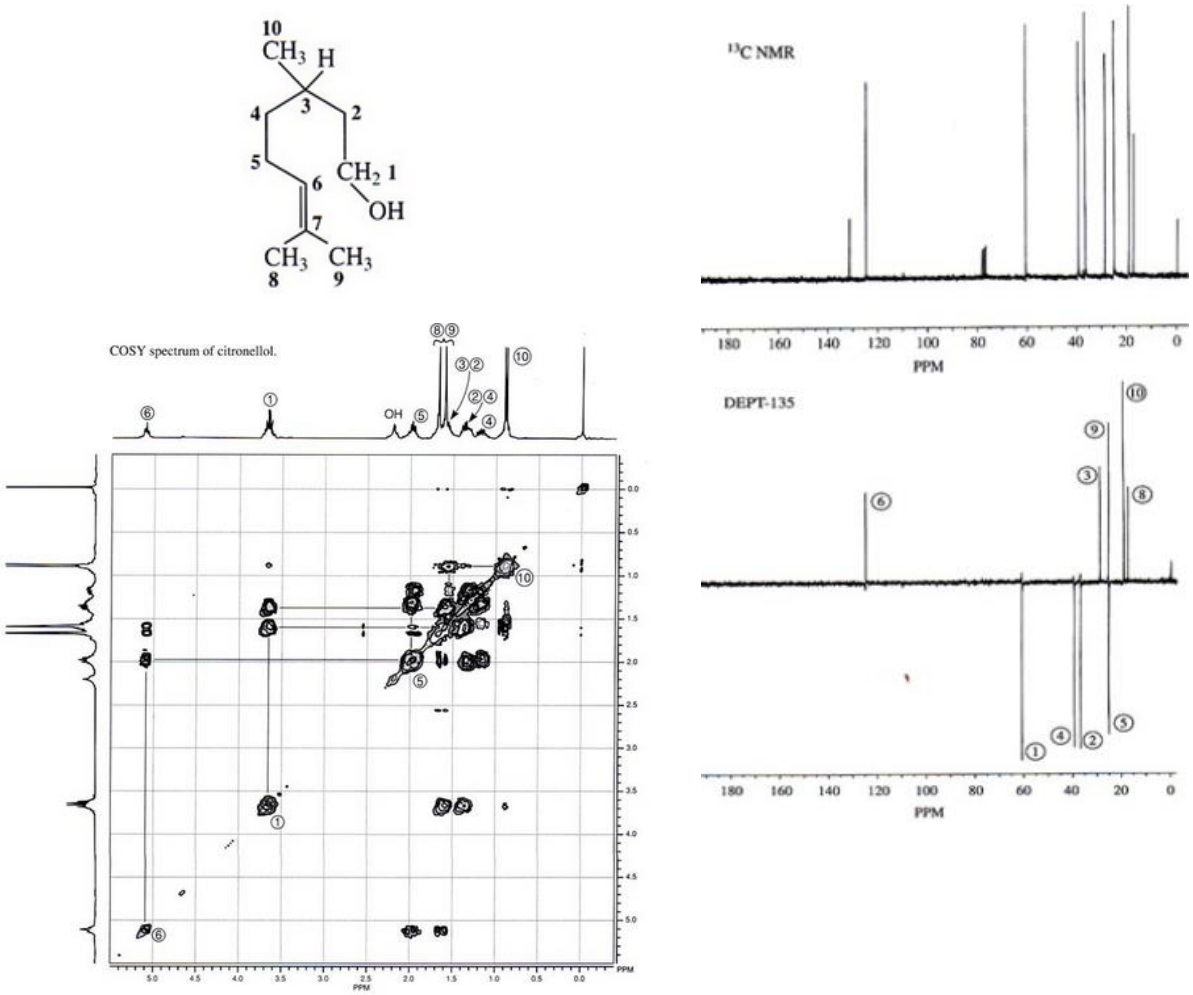
PDC - pyridynium dichromate

SPECTRA

a) FT-IR spectrum of citronellol

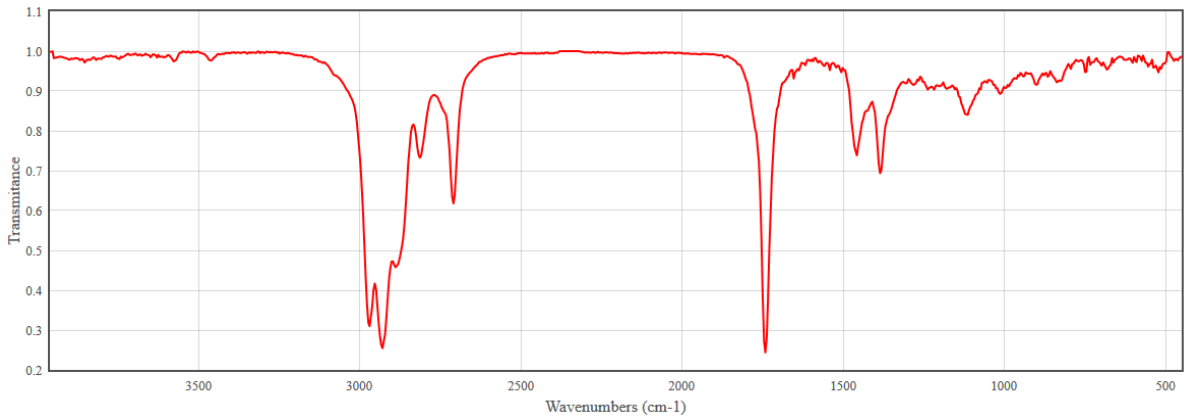


b) ^{1}H NMR and ^{13}C NMR spectra of citronellol in $CDCl_3$.

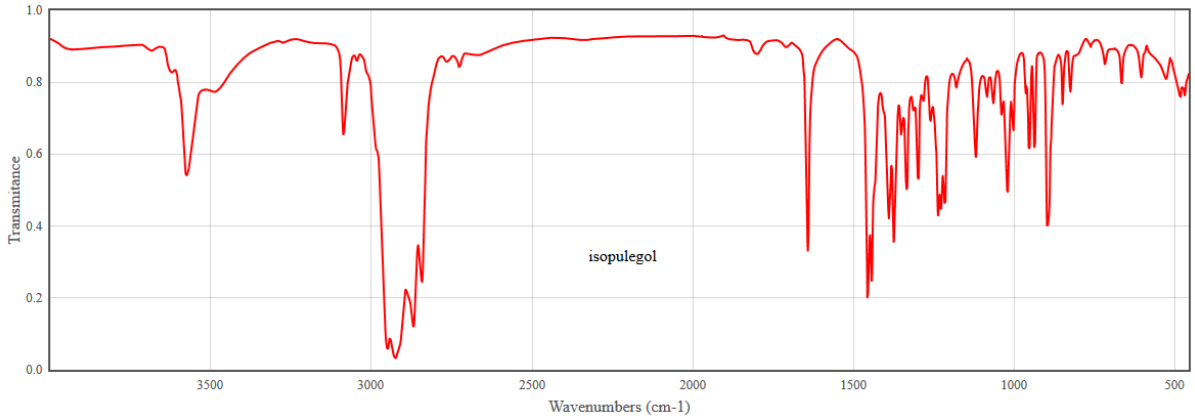


https://orgspectroscopyint.blogspot.com/2014/11/citronellolcosy.html

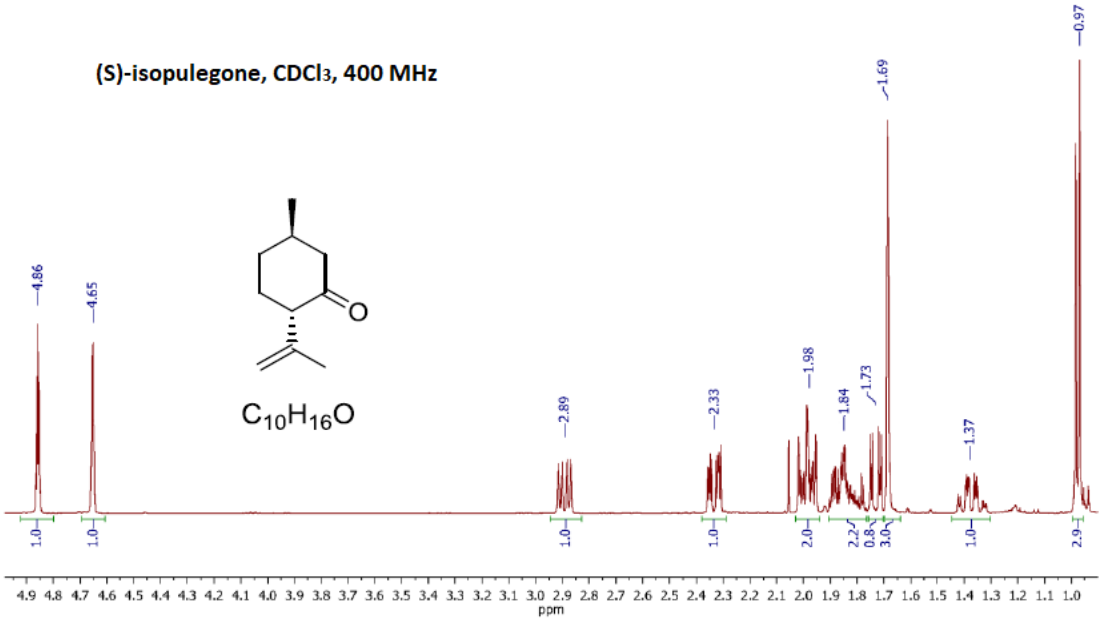
c) FT-IR spectrum of citronellal

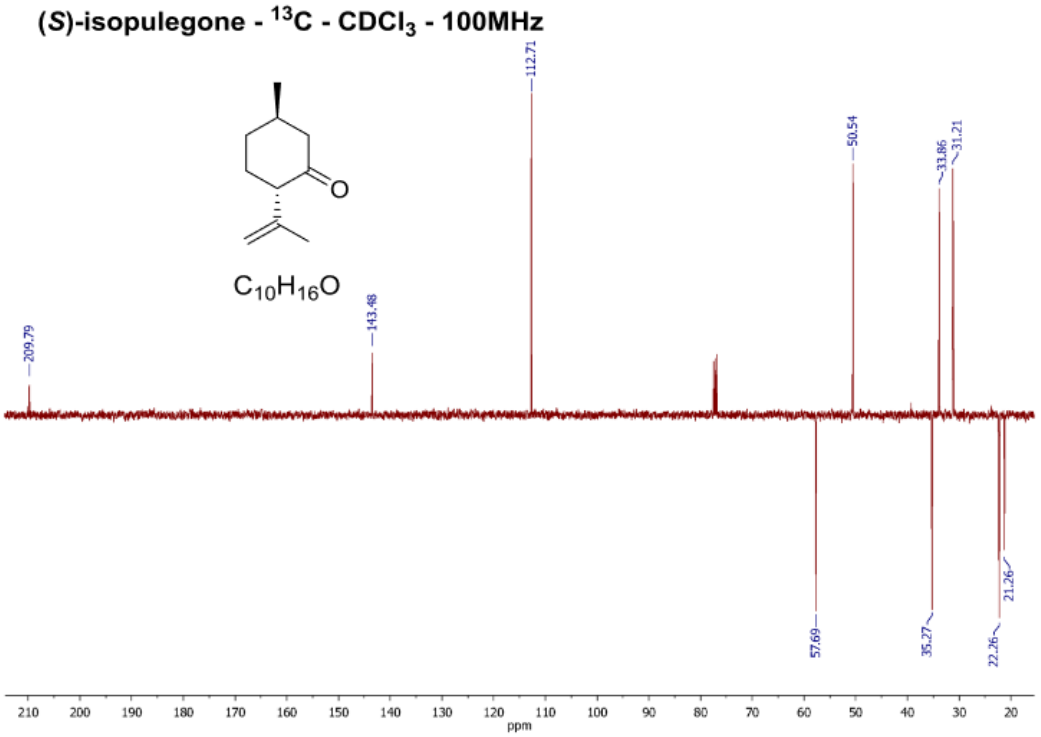


d) FT-IR spectrum of isopulegone



e) ^{1}H NMR and ^{13}C NMR spectra of isopulegone in $CDCl_3$.





References

Black C., Buchanan G. L., Jarvie A. W.: A synthesis of (±)-pulegone. *J. Chem. Soc*. 1956, 2971-2972.

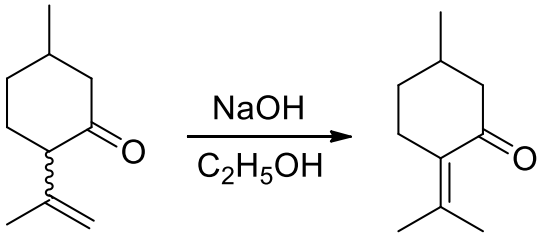
Corey E. J., Ensley H. E., Suggs J. W.: Convenient synthesis of (S)-(-)-pulegone from (-)-citronellol. *Org. Chem.* 1976, 41, 2, 380-381. doi.org/10.1021/jo00864a047

Rigamonti M. G., Gatti F. G.: Stereoselective synthesis of hernandulcin, peroxylippidulcine A, lippidulcines A, B and C and taste evaluation. *Beilstein J. Org. Chem.* **2015,** *11,* 2117–2124. doi:10.3762/bjoc.11.228

https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-228-S1.pdf

https://orgspectroscopyint.blogspot.com/2014/11/citronellolcosy.html

STEP 2 PULEGONE



Reagents:

isopulegone	1.0 g
NaOH	20 mg
CH_2Cl_2	30 mL
10% HCl	
NaCl	
anh. K_2CO_3	
ethanol	

Instrumentation and glassware:

round-bottom flask 50 mL
cooler (condenser)
magnetic stirrer
separatory funnel
glass funnel

In round-bottom flask (50 mL) place 1.0 g of isopulegone, and treat it with the solution of 20 mg NaOH in 10 mL of ethanol. The solution heat under reflux for 1 hour, then evaporate ethanol under reduced pressure.

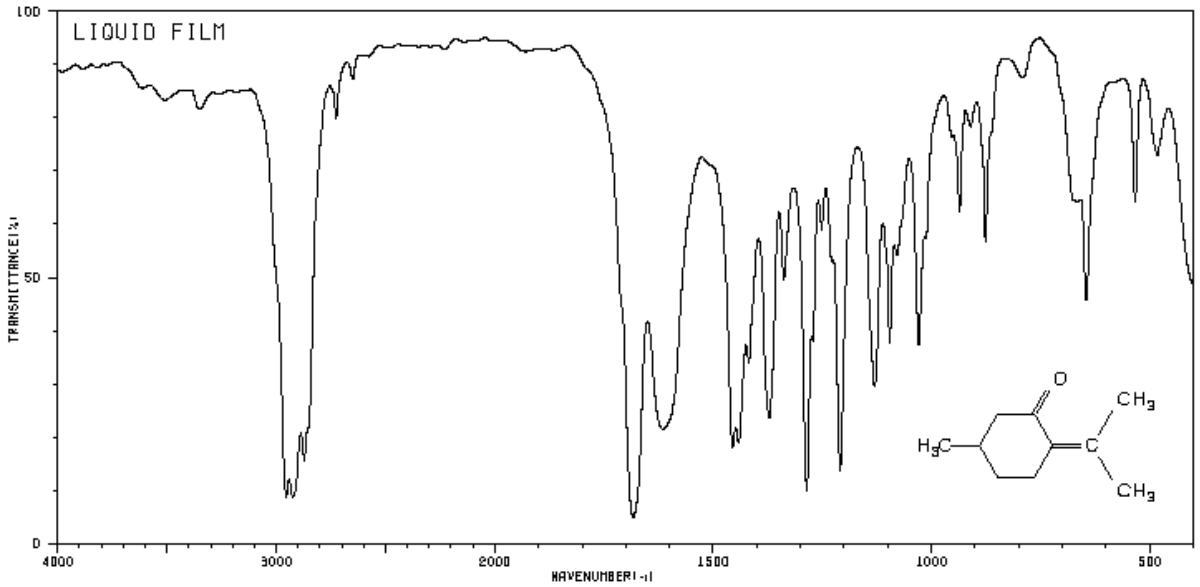
Isolation and purification. Add 10 mL of cold water to the residue, and then 10 mL of diethyl ether. Move the mixture to a separatory funnel and extract with diethyl ether (3 x 10 mL). Combine the organic layers and wash them with 10% HCl, and then with brine. Dry the ether extract over anh. K_2CO_3 (ca. 30 min), then filtrate through the funnel with cotton plug to remove inorganic salt, wash it with diethyl ether. Transfer the combined organic fractions into a clean, dry and **weighted** round-bottom flask (50 mL) and concentrate the solution on rotary evaporator. Weight the crude product, calculate the percentage yield and characterize by TLC, IR and GC-MS. The crude pulegone can be distilled under pressure of 18 mm Hg and collected at 104–106 ^{o}C.

Thin layer chromatography (TLC):

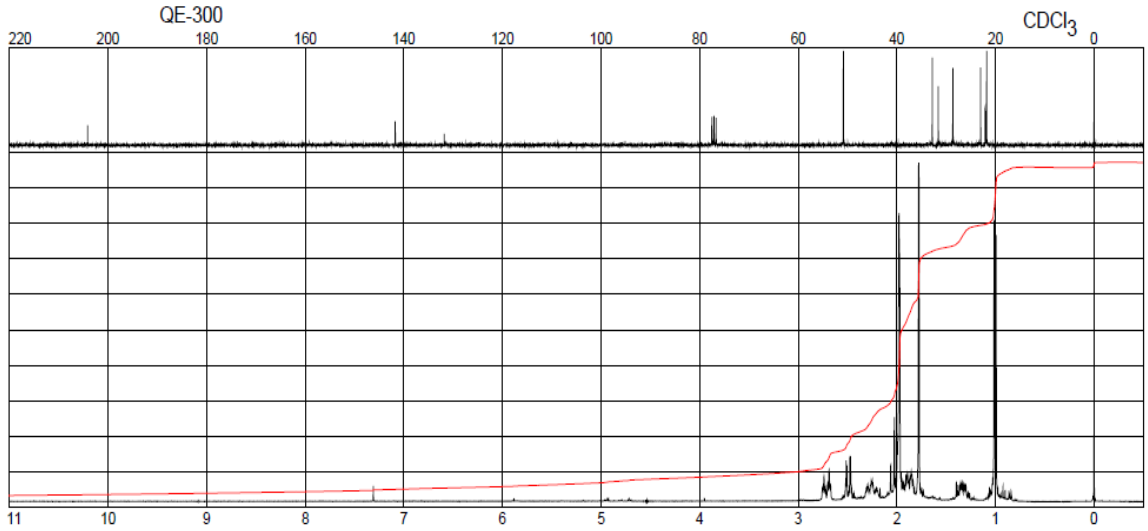
SiO_2 plate develop with *n*-hexane/ethyl acetate (9.5: 0.5, v/v) and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

SPECTRA

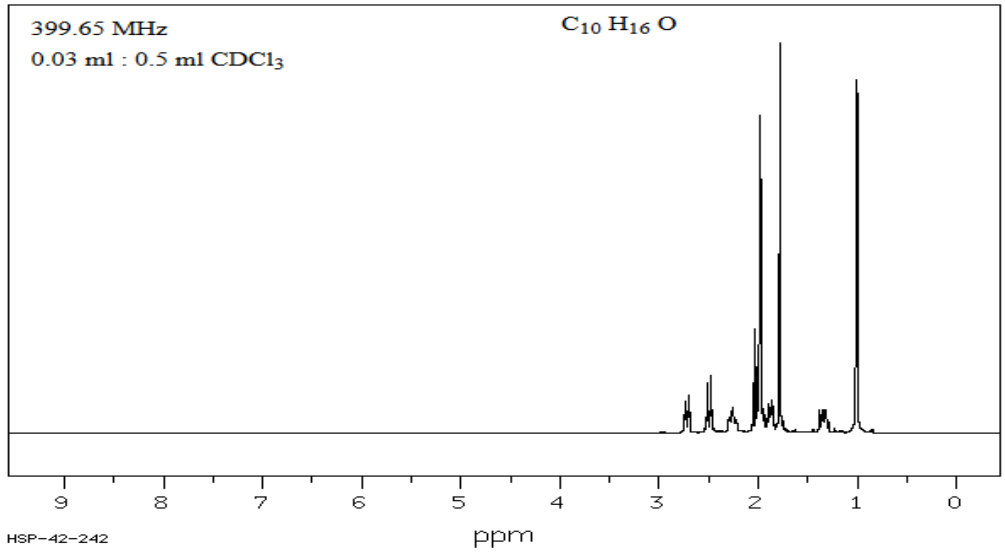
a) FT-IR spectrum of pulegone



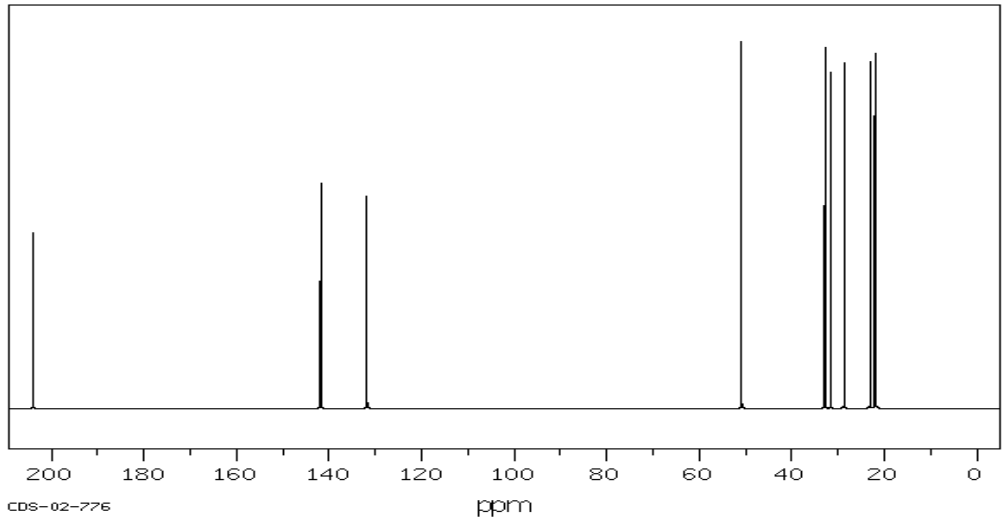
b) ^{1}H NMR and ^{13}C NMR spectra of pulegone in chloroform-*d*



^{1}H NMR spectrum of pulegone in chloroform-*d*



^{13}C NMR spectrum of pulegone in chloroform-*d*



References

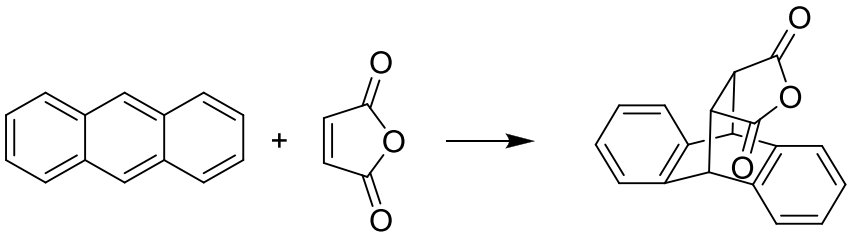
Black C., . Buchanan G. L, W. Jarvie A.: A synthesis of (±)-pulegone. *J. Chem. Soc.* 1956, 2971-2972.

Corey E. J., Ensley H. E., Suggs J. W.: Convenient synthesis of (S)-(-)-pulegone from (-)-citronellol. *Org. Chem.* 1976, 41, 2, 380-381. doi.org/10.1021/jo00864a047

Rigamonti M. G., Gatti F. G.: Stereoselective synthesis of hernandulcin, peroxylippidulcine A, lippidulcines A, B and C and taste evaluation. *Beilstein J. Org. Chem.* **2015,** *11,* 2117–2124. doi:10.3762/bjoc.11.228

https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-228-S1.pdf

6. DIELS-ALDER SYNTHESIS of *CIS*-9,10-DIHYDRO-9,10-DIETHYLENEANTHRACENE-11,12-DICARBOXYLIC ACID ANHYDRIDE (conventional synthesis)



Reagents:

anthracene	249 mg
maleic anhydride	120 mg
xylene (mixture of isomers)	12 mL

Instrumentation and glassware:

magnetic stirrer with heating
magnetic dipole
round-bottom flask 25 mL
condenser
filtering flask with Büchner funnel
crystallizing dish
glass rod
oil bath

Work should be performed under the fume hood!

Place into a 25 mL round-bottom flask equipped with a magnetic stirrer anthracene (249 mg), maleic anhydride (120 mg) and xylene (12 mL). Then heat under reflux in an oil bath (oil temperature about 160 ^{o}C) for 45 minutes. At this time, the yellow color of the solution gradually disappears.

After cooling the mixture, place the flask in an ice bath to crystallize the product (about 30 min). The product in the form of crystals filter on a foam funnel or Büchner funnel. Wash the product with cold methanol (2 x 5 mL) and dry on air. Yield 78%, melting point 261–262 °C.

Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with CH_2Cl_2. Remove the plate and allow the solvent to evaporate. The spot of the product is visible under the UV light.

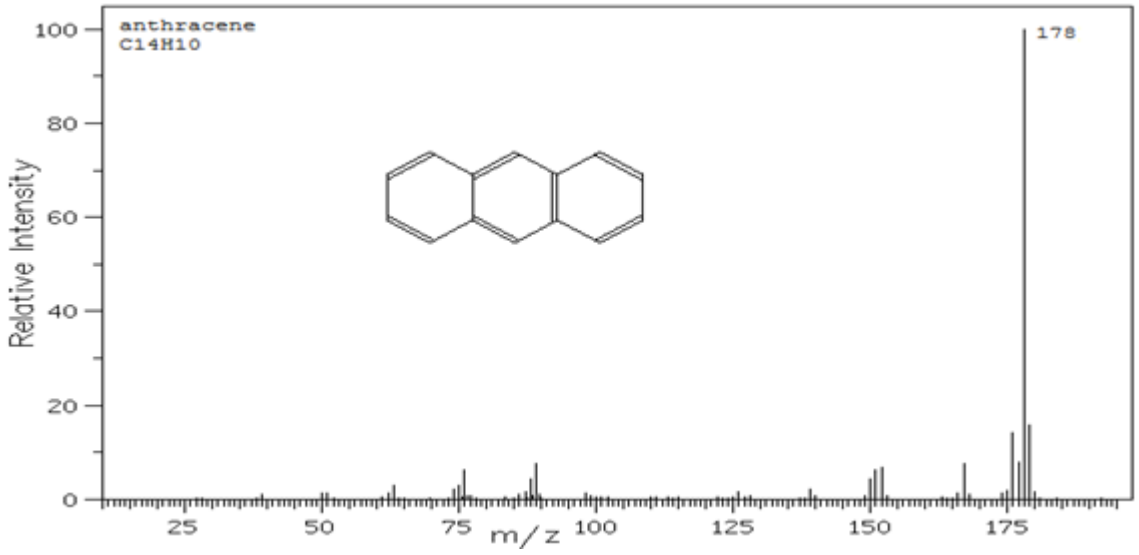
Notes:1) If the product is not pure enough, it can be recrystallized from small amount of ethyl acetate.

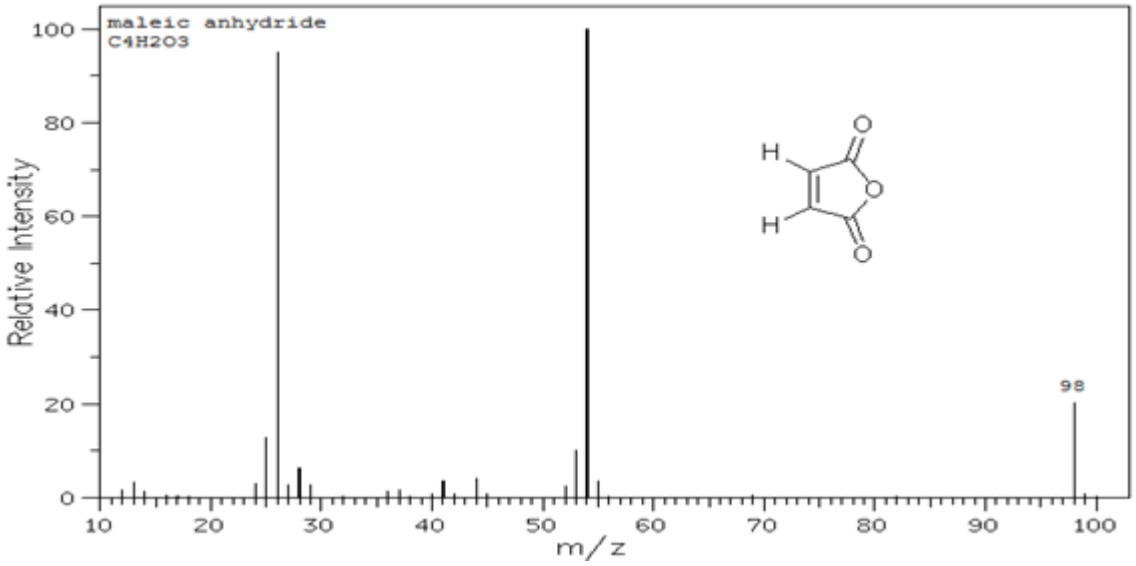
(2) Reaction can also be carried out in a microwave oven (180 °C, 10 min).

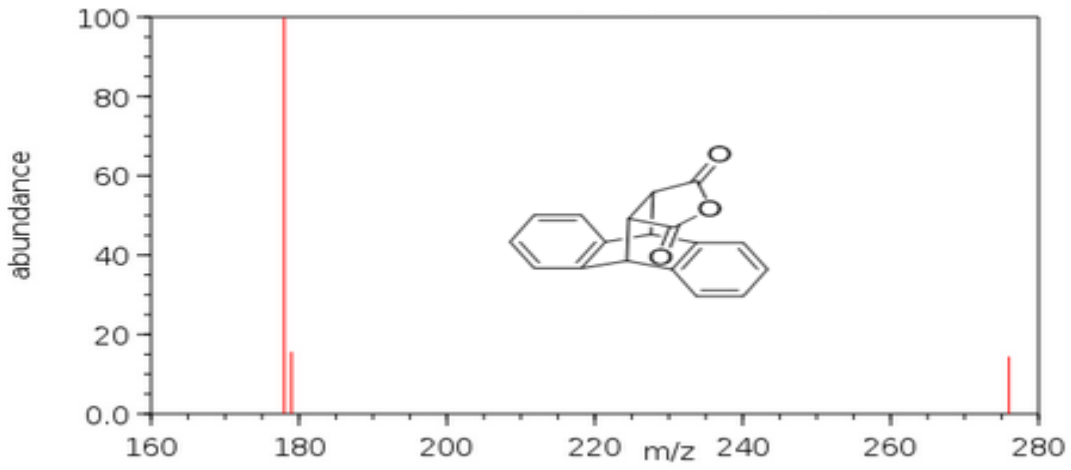
(3) TLC spot may be unclear/expanded, if the eluent is water contaminated due to anhydride ring opening.

SPECTRA

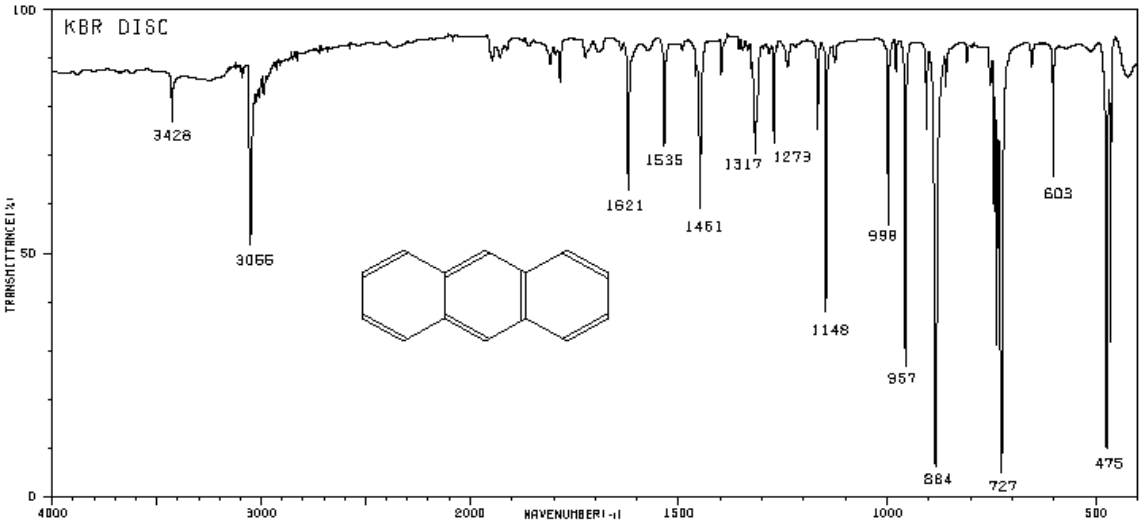
a) MS spectra of anthracene, maleic anhydride and their Diels-Alder adduct

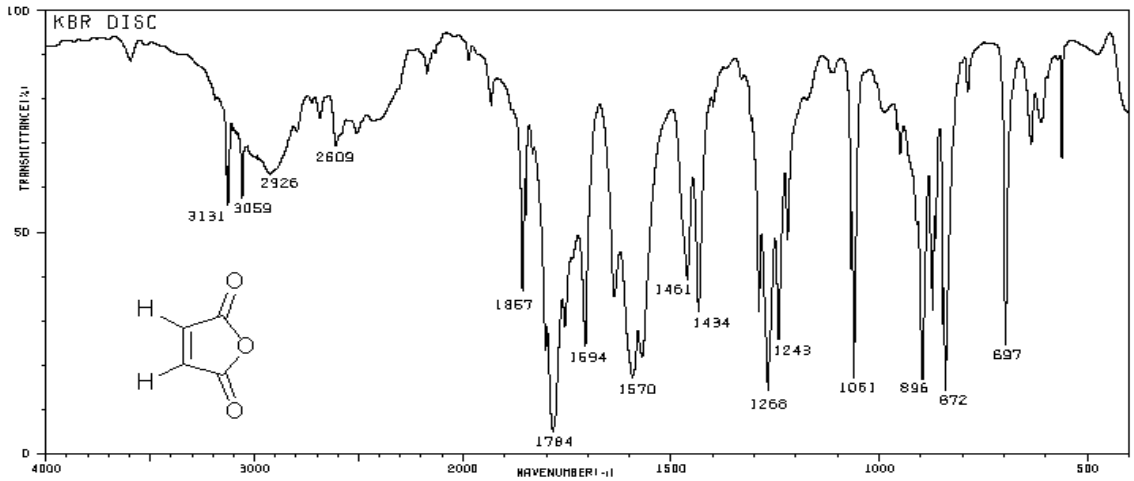


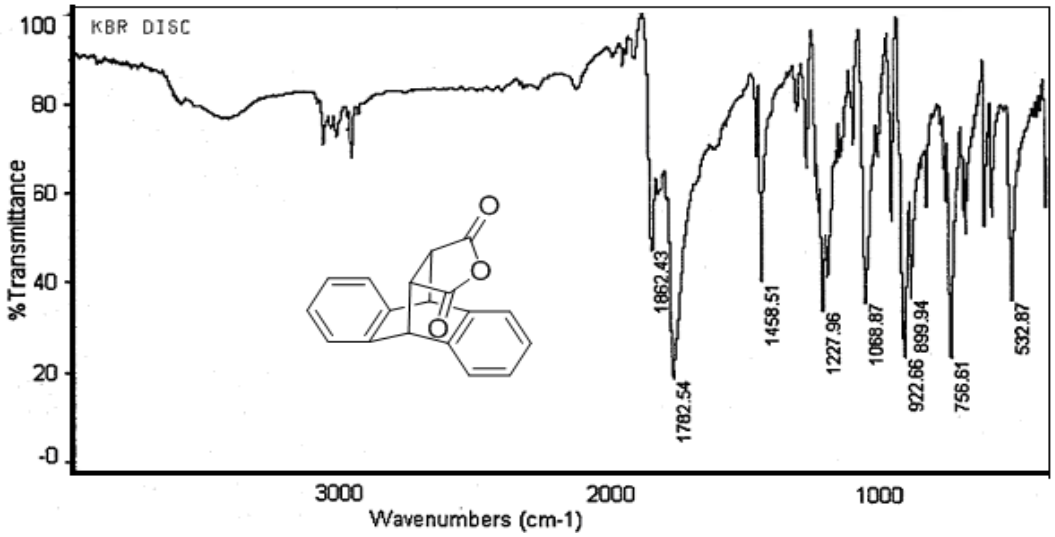




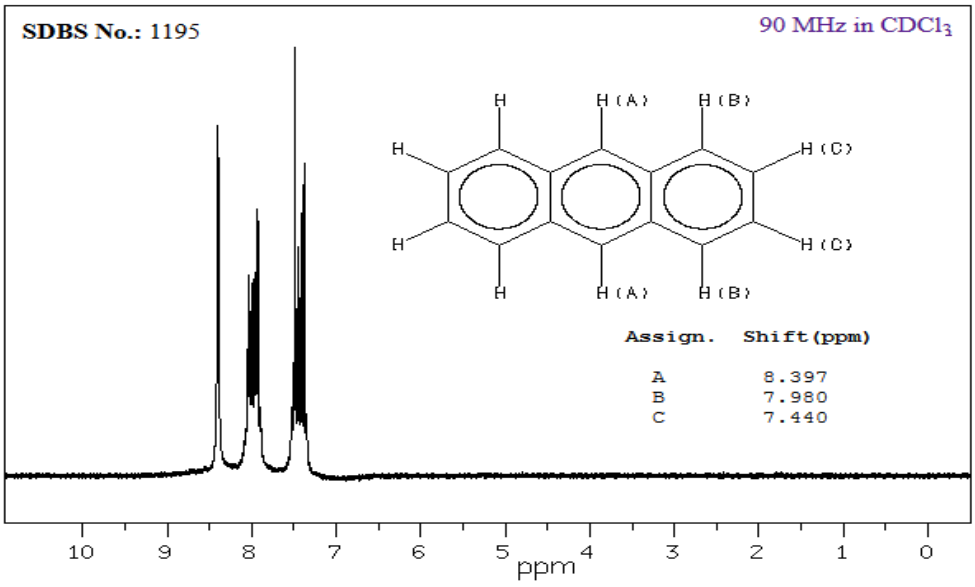
b) FT-IR spectra of anthracene, maleic anhydride and their Diels-Alder adduct.

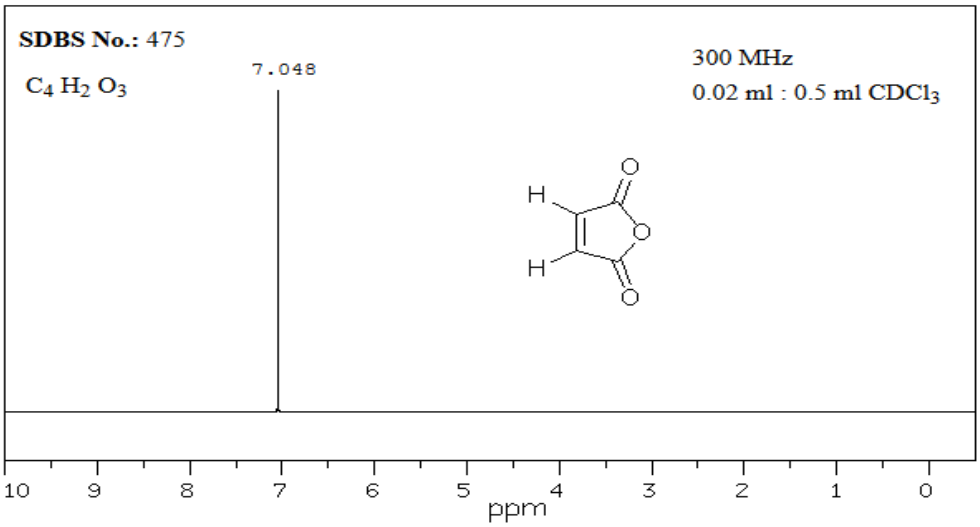


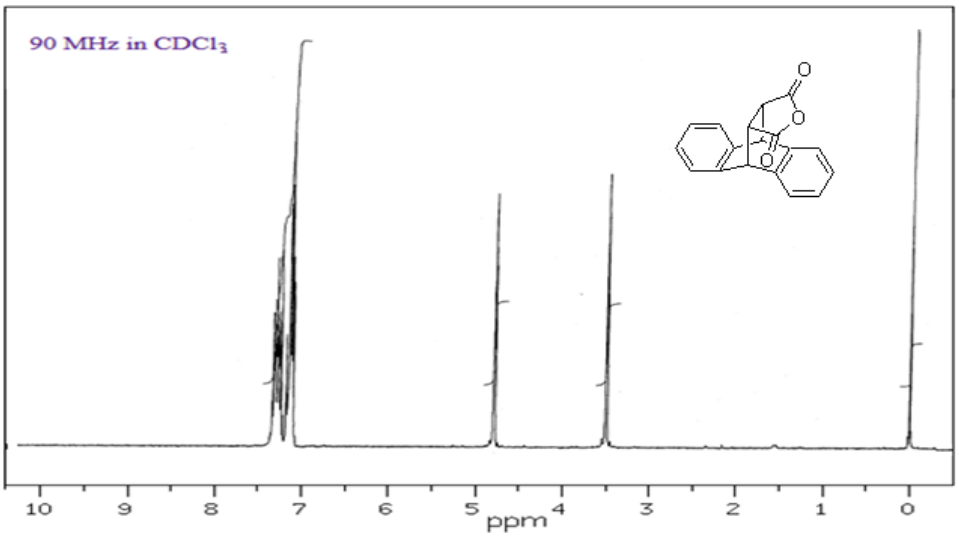




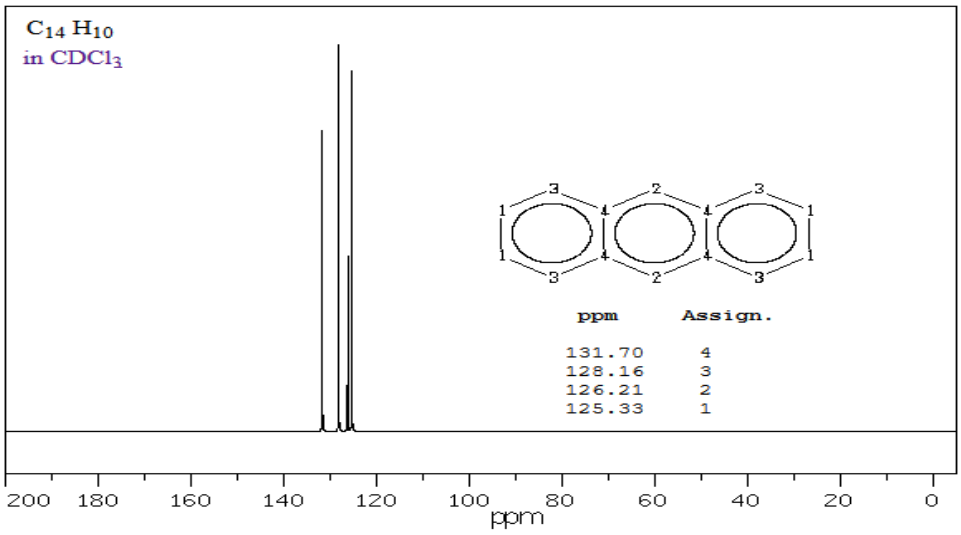
c) ^{1}H NMR spectra of anthracene, maleic anhydride and their Diels-Alder adduct.

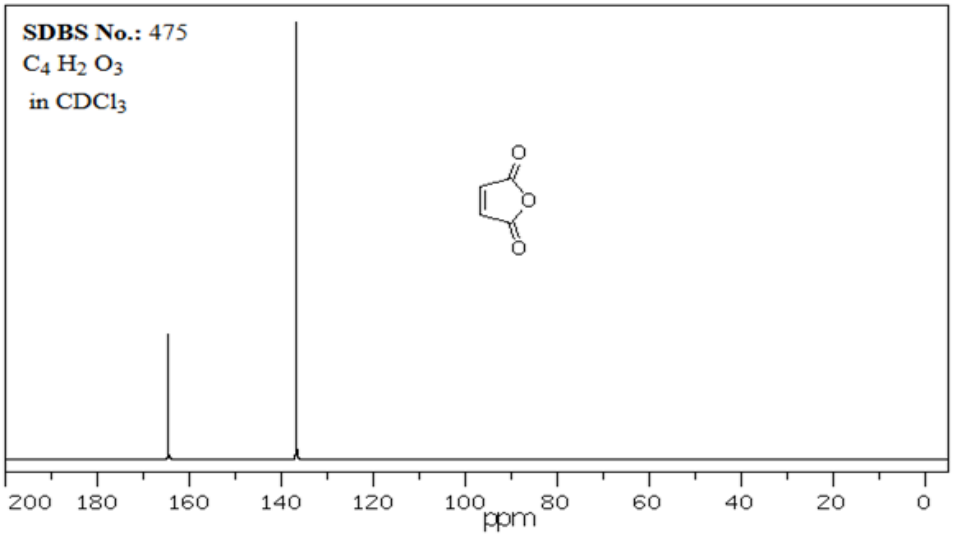


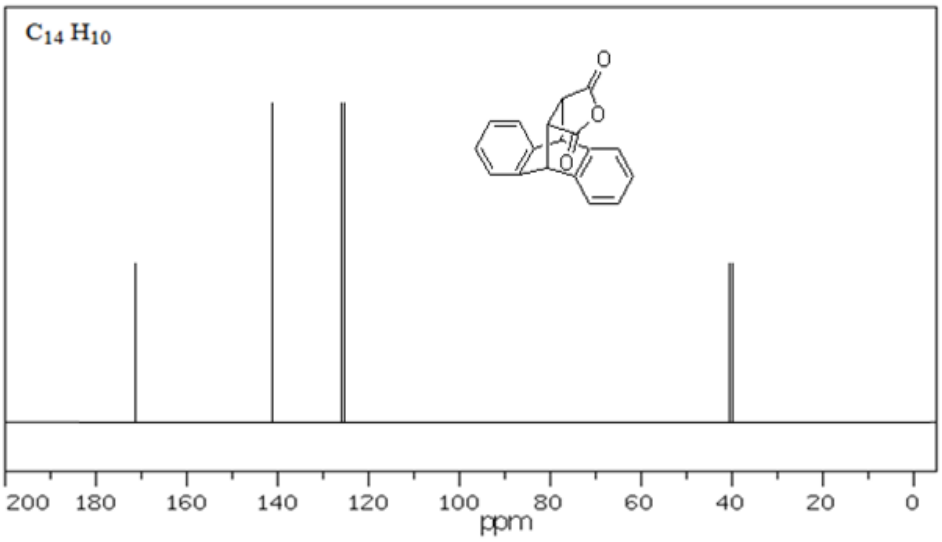




d) ^{13}C NMR spectra of anthracene, maleic anhydride and their Diels-Alder adduct





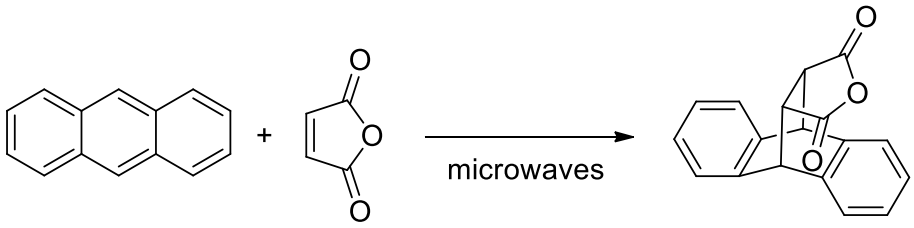


References

Mayo D. W., Pike R. M., Forbes D. C.: Microscale Organic Laboratory: With Multistep and Multiscale Syntheses, 5th Edition, John Wiley & Sons, 2010.

www.chemicalbook.com/SpectrumEN_108-31-6_1HNMR.htm

7. DIELS-ALDER SYNTHESIS of *CIS*-9,10-DIHYDRO-9,10-DIETHYLENEANTHRACENE-11,12-DICARBOXYLIC ACID ANHYDRIDE (microwave-assisted synthesis)



Reagents:

anthracene	249 mg
maleic anhydride	120 mg
xylene (mixture of isomers)	6 mL

Instrumentation and glassware:

microwave vial
filtering flask with Büchner funnel
crystallizing dish
glass rod
ice bath

The mixture of anthracene (249 mg) with maleic anhydride (120 mg) ground thoroughly in a mortar, and then transfer to a microwave vial. After the addition of 6 mL of xylene, shake gently the mixture.

Place the closed vial in the microwave oven. The irradiation was carried out for 10 min at a 180 °C. After cooling the mixture, place the vial in an ice bath to crystallize the product (about 30 min). The product in the form of crystals filter on a foam funnel or Büchner funnel. Wash the product with methanol (2 x 5 mL) and dry on air. Yield 80%, melting point 261–262 °C.

Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with CH_2Cl_2. Remove the plate and allow the solvent to evaporate. The spot of the product is visible under the UV light.

Notes:

1) If the product is not pure enough, it can be recrystallized from small amount of ethyl acetate.
(2) TLC spot may be unclear/expanded, if the eluent is water contaminated due to anhydride ring opening.

SPECTRA

MS, **FT-IR** and **NMR** spectra of anthracene, maleic anhydride and their Diels-Alder adduct find in chapter 6.

References

Bari S.S., Bose A. K., Chaudhary A.G., Manhas M. S., Raju V. S., Robb A. W.: Solvent free synthesis of N-Sulfonylimines using microwave Irradiation, *J. Chem. Ed*. 1992, 69 (11), 938.

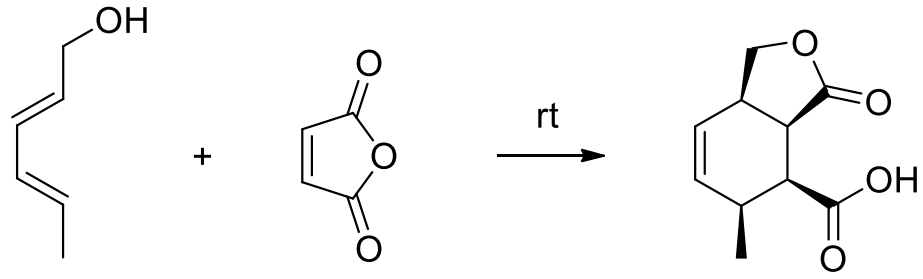
Mayo D. W., Pike R. M., Forbes D. C.: Microscale Organic Laboratory: With Multistep and Multiscale Syntheses, 5th Edition, John Wiley & Sons, 2010.

https://sdbs.db.aist.go.jp/sdbs/

https://pubchem.ncbi.nlm.nih.gov/com.p.ound/Anthracene-maleic-anhydride-diels-alder-adduct#section=Mass-Spectrometry&fullscreen=true

https://archives.library.illinois.edu/erec/University%20Archives/1505050/chem337/onlinesyllabus/onlinesyllabus/chem337Expt10B_rxn_anthracene.html

8. DIELS-ALDER SYNTHESIS of 1,3,3a,4,5,7a-HEXAHYDRO-5-METHYL-3-OXO-4-ISOBENZOFURANCARBOXYLIC ACID



Reagents:

(*2E,4E*)-2,4-hexadien-1-ol
maleic anhydride
water

Instrumentation and glassware:

beakers
Pasteur pipette
test tubes
thermometer
stopwatch

Caution!

It is strongly exothermic reaction – work under fume hood. Wear gloves and googles (face shield)!

Experiment 1. Reactions of maleic anhydride with solid and liquid (*2E,4E*)-2,4-hexadien-1-ol on 5.0 mmol scale.

5.0 mmol (0.49 g) of solid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the first beaker and the same amount of liquid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the second beaker. To each beaker, 5.0 mmol (0.49 g) of finely ground maleic anhydride is added. A temperature probe is inserted into each beaker and measurements are taken for 10 minutes.

Experiment 2. Reactions of maleic anhydride with solid and liquid (*2E,4E*)-2,4-hexadien-1-ol on 10.0 mmol scale.

10.0 mmol (0.98 g) of solid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the first beaker and the same amount of liquid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the second beaker. To each beaker, 10.0 mmol (0.98 g) of finely ground maleic anhydride is added. A temperature probe is inserted into each beaker and measurements are taken for 10 minutes.

Experiment 3. Reactions of maleic anhydride with solid (*2E,4E*)-2,4-hexadien-1-ol on 10.0 mmol scale in a dry and a wet beaker.

10.0 mmol (0.98 g) of solid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the first beaker and the same amount of solid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the second beaker. Water (0.70 mL) was added to the second beaker. To each beaker, 10.0 mmol (0.98 g) of finely ground maleic anhydride is added. A temperature probe is inserted into each beaker and measurements are taken for 10 minutes.

Experiment 4. Reactions of maleic anhydride with liquid (*2E,4E*)-2,4-hexadien-1-ol on 10.0 mmol scale in a dry and a wet beaker.

10.0 mmol (0.98 g) of liquid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the first beaker and the same amount of liquid (2E,4E)-2,4-hexadien-1-ol is weighed into the second beaker. Water (0.70 mL) was added to the second beaker. To each beaker, 10.0 mmol (0.98 g) of finely ground maleic anhydride is added. A temperature probe is inserted into each beaker and measurements are taken for 10 minutes.

Experiment 5. Reactions of maleic anhydride with solid and liquid (2E,4E)-2,4-hexadien-1-ol on 10.0 mmol scale in a test tube.

10.0 mmol (0.98 g) of solid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the first test tube and the same amount of liquid (*2E,4E*)-2,4-hexadien-1-ol is weighed into the second test tube. To each test tube, 10.0 mmol (0.98 g) of finely ground maleic anhydride is added. A temperature probe is inserted into each test tube and measurements are taken for 10 minutes. After the violent reaction in each test tube subsides, each test tube is shaken to mix the layers that have formed (**Fig**. **3**).

Figure 3. Two layers formed in a reaction in a test tube.
(source: B.A. Parsons, V. Dragojlovic: Demonstration of a runaway exothermic reaction: Diels-Alder reaction of (*2E*,*4E*)-2,4-hexadien-1-ol and maleic anhydride, *J. Chem. Educ.* 88 (2011) 1553–1557).

Please note:

At room temperature, (*2E,4E*)-2,4-hexadien-1-ol is in the form of a soft waxy solid accompanied by a liquid. By tilting the bottle and waiting for a while one can collect a considerable amount of

the liquid. Alternatively, to facilitate transfer of liquid (*2E*,*4E*)-2,4-hexadien-1-ol, the bottle can be warmed (m.p. = 28–33 °C). Solid (*2E*,*4E*)-2,4-hexadien-1-ol is rather difficult to get out of the bottle and weigh accurately. Therefore, (*2E*,*4E*)-2,4-hexadien-1-ol should be weighed directly into the reaction vessel.

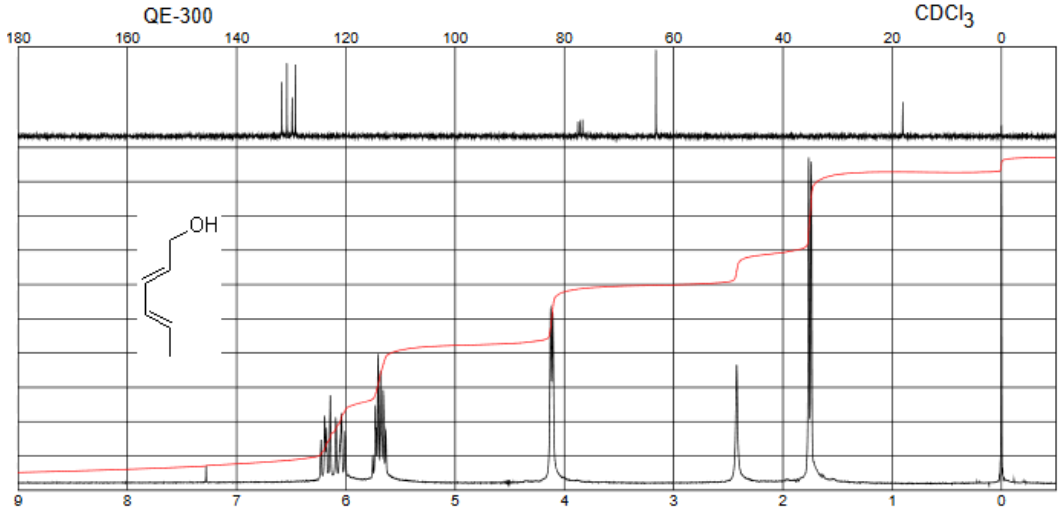
Student report:

1. What is the effect of the increased scale on each of the reactions?
2. What is the effect of water on the rate of reaction of solid (*2E*,*4E*)-2,4-hexadien-1-ol with maleic anhydride?
3. What is the effect of water on the reaction temperature of (*2E*,*4E*)-2,4-hexadien-1-ol with maleic anhydride?
4. What is the effect of shape and size of the reaction vessel on the rate of reaction of each solid and liquid (*2E*,*4E*)-2,4-hexadien-1-ol with maleic anhydride?
5. Explain why in the work up of some aromatic substitution reactions we pour the reaction mixture, which contains concentrated sulfuric acid, onto crushed ice instead of liquid water.

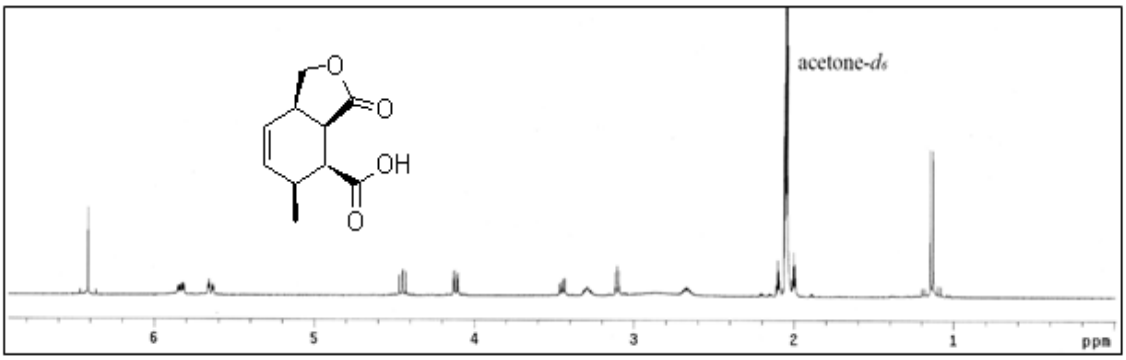
SPECTRA

a) **Spectra of maleic anhydride** find in chapter 6. Diels-Alder Product.

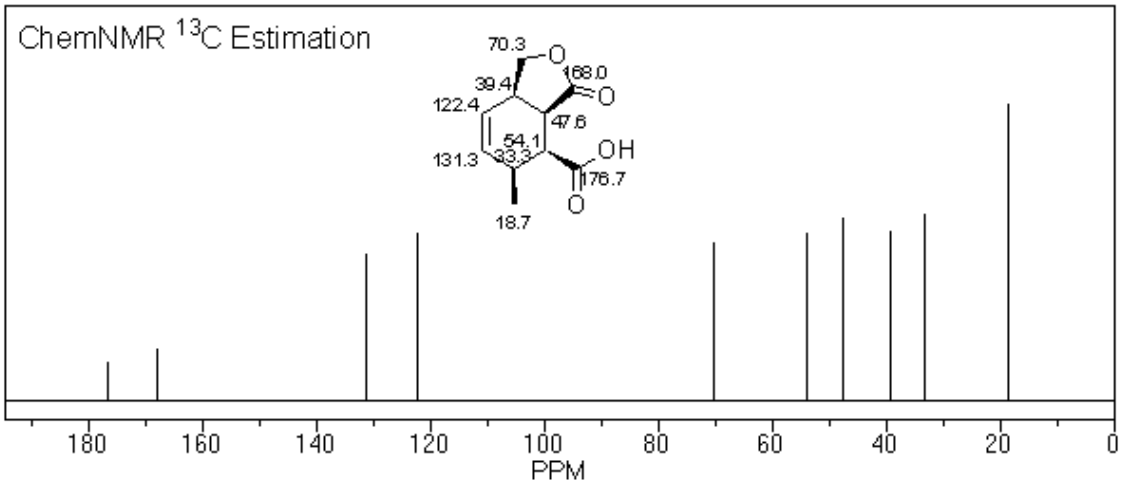
b) ^{1}H and ^{13}C NMR spectra of (*2E*,*4E*)-2,4-hexadien-1-ol



c) ^{1}H NMR spectrum of 1,3,3a,4,5,7a-hexahydro-5-methyl-3-oxo-4-isobenzofurancarboxylic acid in acetone-d_6.



d) ^{13}C NMR spectrum of 1,3,3a,4,5,7a-hexahydro-5-methyl-3-oxo-4-isobenzofurancarboxylic acid
- estimation



f) FT IR characteristic absorbances:

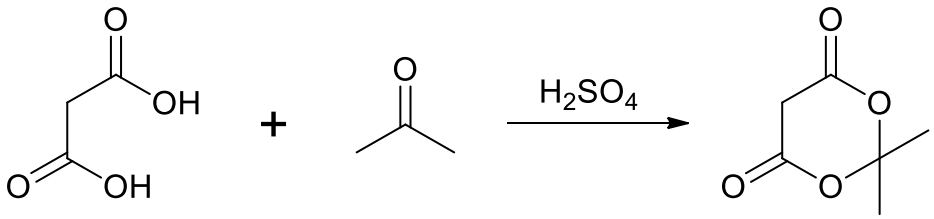
of (*2E*,*4E*)-2,4-hexadien-1-ol:
ν C=C (diene) 1600-1650 cm-1
ν O-H 3200 – 3400 cm-1

of 1,3,3a,4,5,7a-hexahydro-5-methyl-3-oxo-4-isobenzofurancarboxylic acid (D-A Adduct):
ν C=O (lactones) 1720-1735 cm-1
ν C=O (carboxylic acid) 1720-1730 cm-1
ν O-H 3200 – 3600 cm-1

References

Parsons B.A., Dragojlovic V.: Demonstration of a runaway exothermic reaction: Diels-Alder reaction of (*2E*,*4E*)-2,4-hexadien-1-ol and maleic anhydride, *J. Chem. Educ*. 88, 2011, 1553–1557.

9. MELDRUM'S ACID



Reagents:

malonic acid	5.2 g
acetic anhydride	6 mL
conc. H_2SO_4	0.15 mL
acetone	4 mL

Instrumentation and glassware:

round-bottom flask 25 mL
condenser
filtering flask with Büchner funnel
measuring pipette
crystallizer
mortar

Acetone (ca. 4 mL), malonic acid (5.2 g), and conc. H_2SO_4 (0.15 mL) are placed into a round-bottom flask at 0 °C (ice bath). The **preferred order of addition is acetone first, malonic acid second, and the acid catalyst third.** Addition of acid catalyst last minimizes the possibility of any undesired side reaction between acetone and the acid catalyst.

Isolation and purification. The stirred mixture forms a slurry. The slurry is allowed to stand max. for 1–2 hours. The longer the reactants of step 1 are allowed to stand together, the greater the probability of discoloration due to the presence of color bodies. Such discoloration may be undesired where the Meldrum's acid is to be used in applications wherein color is an important characteristic. However, the color bodies have not altered the purity assay of Meldrum's acid, and do not appear to be more than about one percent of the total composition of isolated Meldrum's acid.

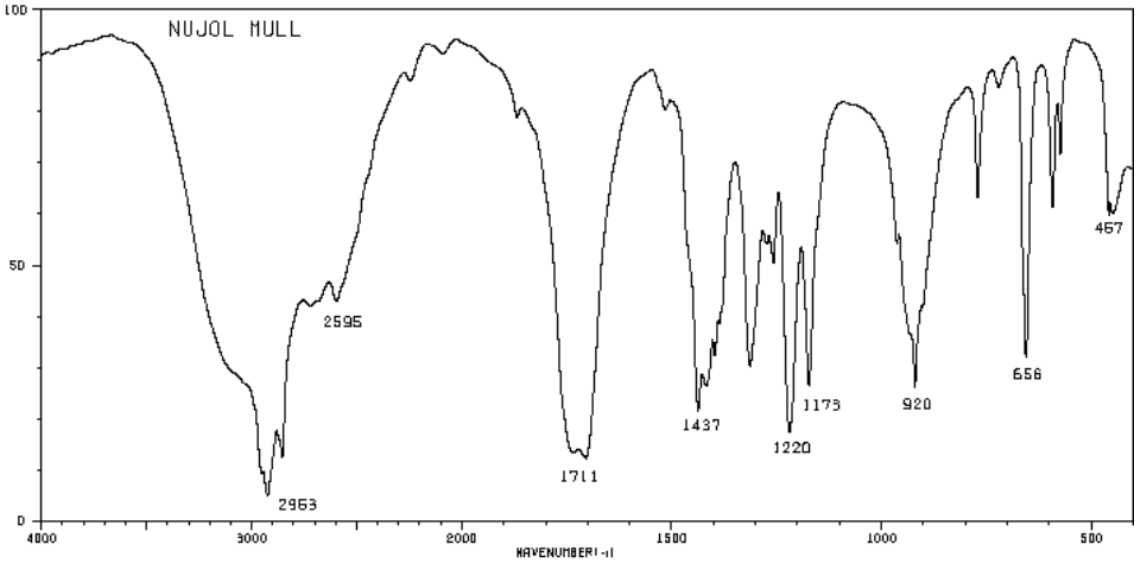
Within half of an hour, add of acetic anhydride (ca. 6 mL) dropwise at a rate of approximately 0.2 mL/min. The mixture begins as a white slurry, and gradually turns pale yellow by the end of the addition of acetic anhydride; this addition is completed after 30 minutes. The mixture is allowed to sit with stirring at 0 °C for 1 hour. After such time the mixture is an orange slurry, that leave in a freezer at –20°C for one week.

Filter the mixture from the flask with *n*-hexane, ground the solid material in a mortar, and then once more filter and rinse with cold (0 °C) 0.5 M H_2SO_4, cold water (5 x 5 mL), and additionally with *n*-hexane, and allow to air dry.

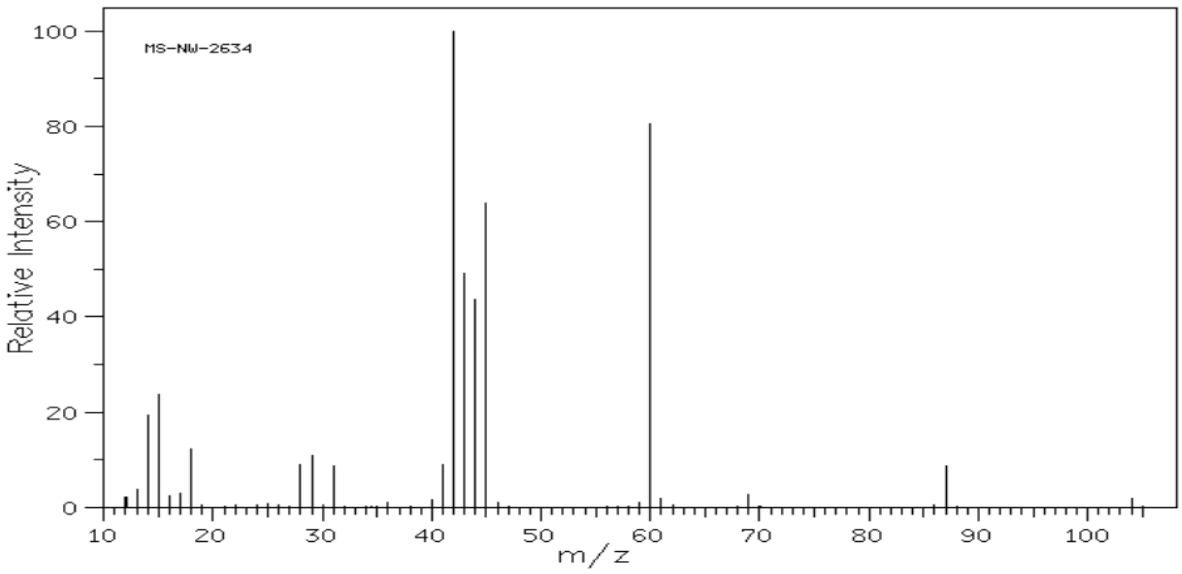
Recrystallized Meldrum's acid from the methyl *tert*-butyl ether (white crystals, m.p. 95-96 °C or from the acetone/diethyl ether/petroleum ether (1:1:1) mixture to get the crystals characterized by m.p. 88-92 °C.

SPECTRA

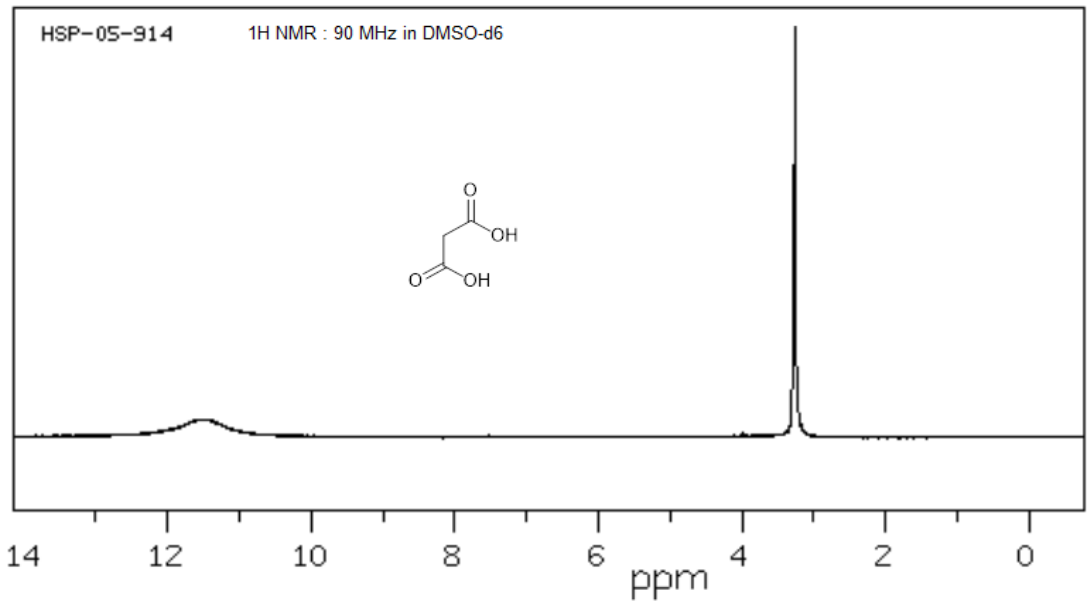
a) FT-IR spectrum of malonic acid in nujol.



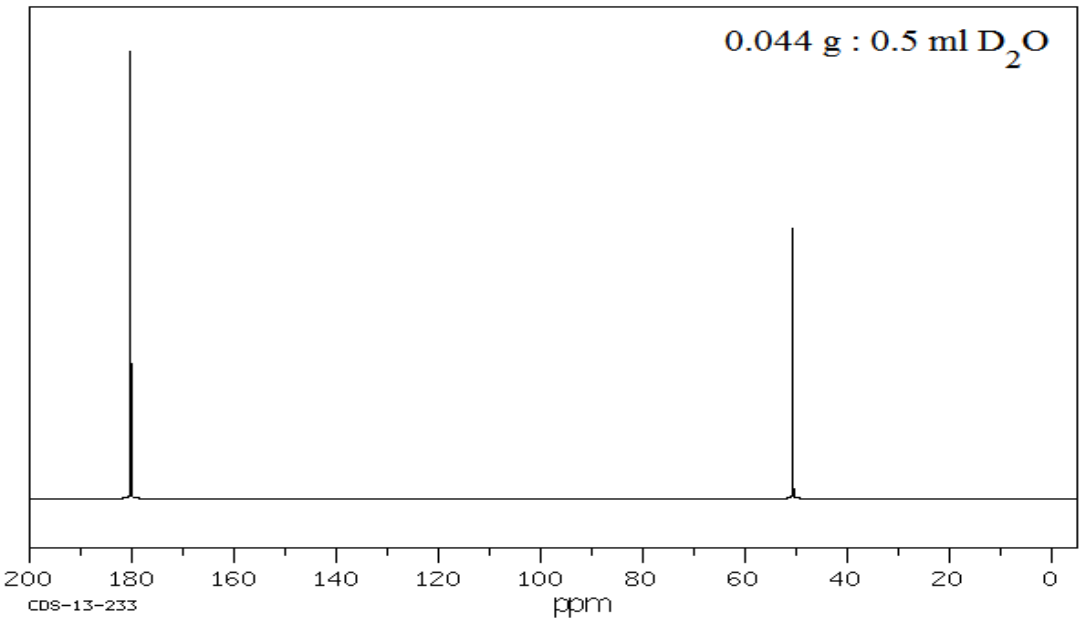
b) EI-MS of malonic acid



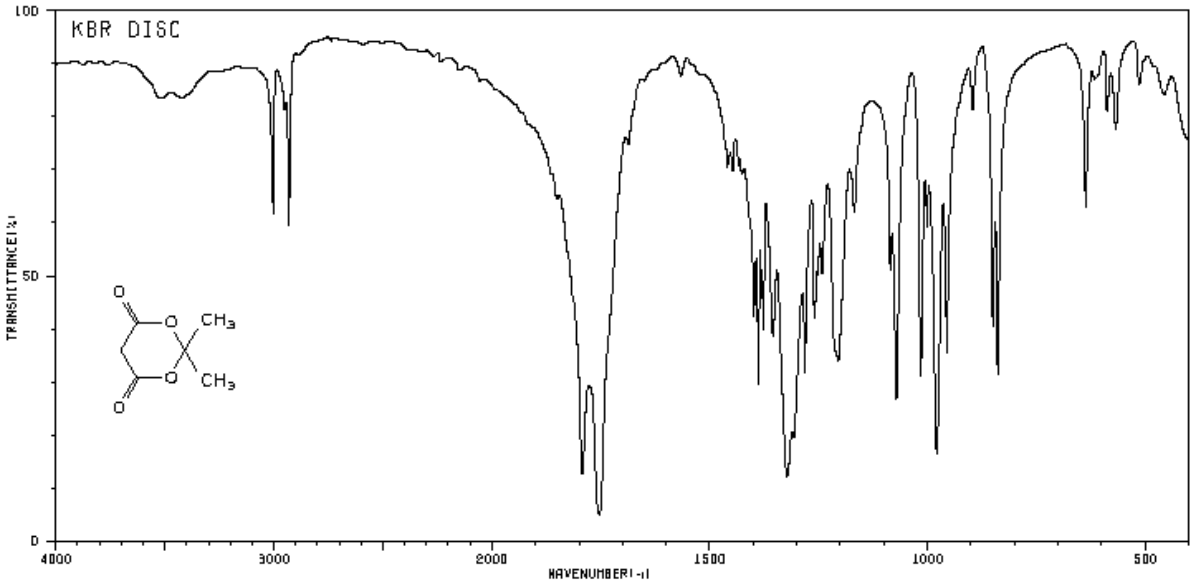
c) ^{1}H and ^{13}C NMR spectra of malonic acid in dimethyl sulfoxide-*d*$_6$.



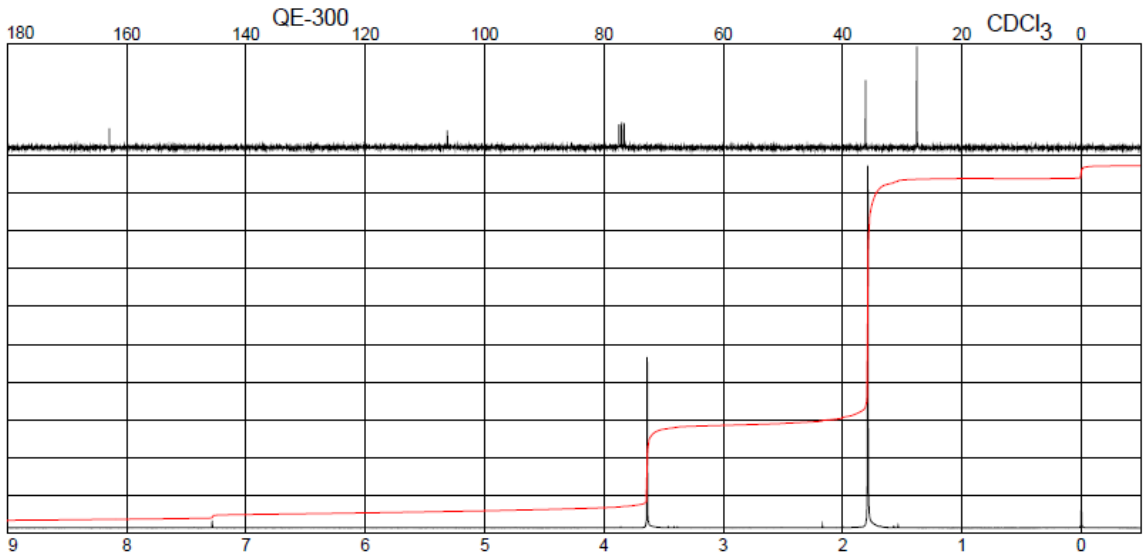
d) ^{13}C NMR spectra of malonic acid in D_2O.



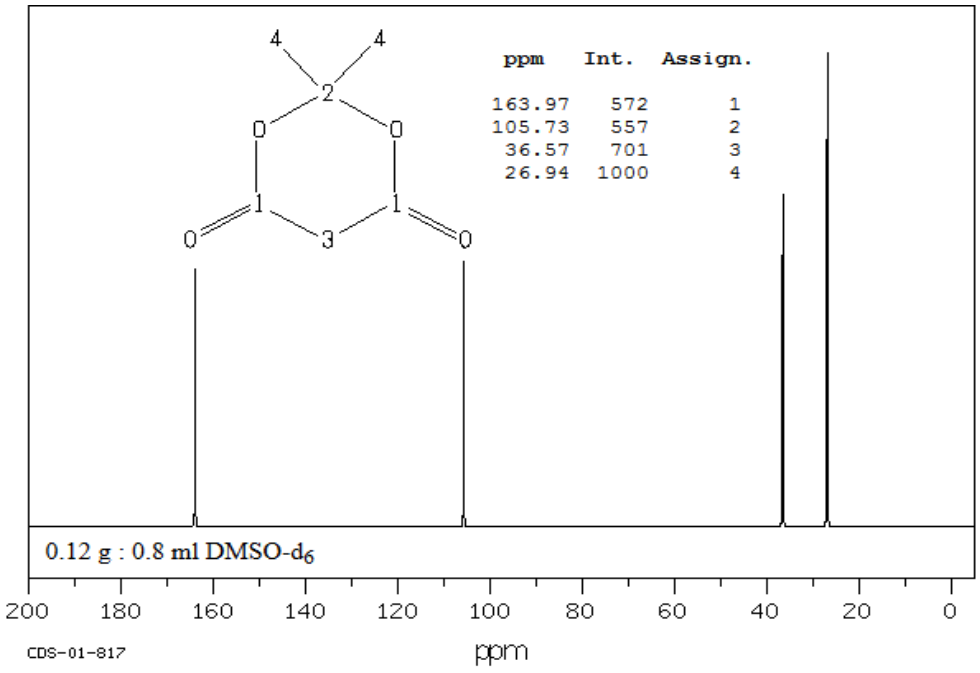
d) FT-IR spectrum of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid).



e) ^{1}H and ^{13}C NMR spectra of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in chloroform-*d* and dimethyl sulfoxide-d_6



f) ^{13}C NMR spectra of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in DMSO-d_6



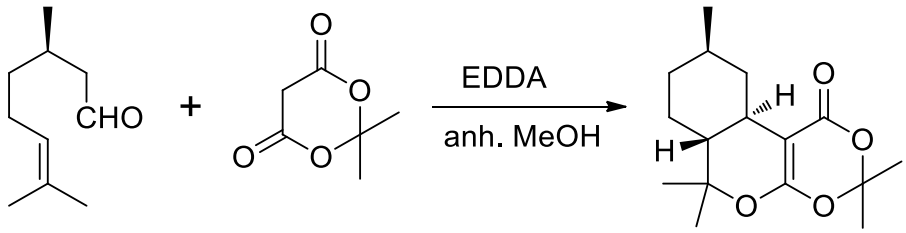
References

http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, date of access) (SDBS No.:2569)

https://www.ebiochemicals.com/Wiki/QcEB000031998_HNMR_1.html

https://www.chemicalbook.com/SpectrumEN_141-95-7_13CNMR.htm

10. DIELS-ALDER SNTHESIS
MELDRUM'S ACID WITH CITRONELLAL



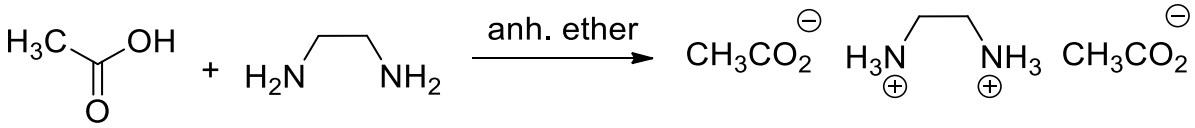
Reagents:

Meldrum's acid	7.92 g
EDDA	0.36 g
anh. methanol	120 mL
(*R*)-(+)-citronellal	7.72 g
diethyl ether	300 mL
NaCl	
$NaHCO_3$	

Instrumentation and glassware:

two-necked round-bottom flask 250 mL
dropping funnel
separatory funnel
filtering flask with Büchner funnel
measuring cylinder
crystallizer

SYNTHESIS OF EDDA



Reagents:

ethylenediamine	12 g
acetic acid	24 g
anh. diethyl ether	120 mL
diethyl ether	

Instrumentation and glassware:

round-bottom flask 250 mL
condenser
filtering flask with Büchner funnel
measuring cylinder
crystallizer

Ethylenediammonium diacetate (EDDA) synthesis:

EDDA is prepared in a 250 mL round-bottom flask with a stirring bar and a pressure-equalizing dropping funnel with a calcium-sulfate-filled drying tube that is charged with dry ethylenediamine (12.0 g) and dry diethyl ether (100 mL).

Isolation and purification. Acetic acid (24.0 g) in dry diethyl ether (20 mL) is added through the dropping funnel to the stirred solution. The reaction mixture is left at 4 °C for 14 hours, and the crystals are collected by filtration and washed with diethyl ether.
Recrystallize crude EDDA from methanol, m.p. 114 °C, as white needles.

SPECTRA

FT IR (KBr): 3500–2000 (NH), 2180 (NH_3), 1650 (C=O), 1600–1400 (COO^-) cm^{-1}
^1H NMR ($CDCl_3$) δ: 1.90 (s, 6 H, CH_3), 3.20 (s, 4 H, CH_2), 5.75 (s, 6 H, NH_3) ppm

DIELS-ALDER SYNTHESIS

A 250 mL round-bottom flask equipped with a pressure-equalizing addition funnel with a calcium-sulfate-filled drying tube, a nitrogen inlet, and a magnetic stirring bar is charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, 7.92 g), a catalytic amount of EDDA (0.36 g, ethylenediammonium diacetate is the best catalyst for this condensation), and dry methanol (100 mL).
(*R*)-(+)-citronellal (7.72 g, $[\alpha]_D$= +13°; dried and distilled under nitrogen at b.p. 83–85°C at 11 mm Hg) is added under nitrogen over 15 min through the dropping funnel to the well-stirred mixture, while the temperature is kept at 10-15°C by cooling the flask with a water bath. The solution is stirred for an additional 45 min at room temperature.

Isolation and purification. The solvent is removed on a rotary evaporator (25 °C), and the remaining yellow oil is dissolved in diethyl ether (300 mL). The organic layer is washed with water (50 mL), saturated with $NaHCO_3$ (2 × 50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. Filtrate the drying agent and evaporate the solvent.

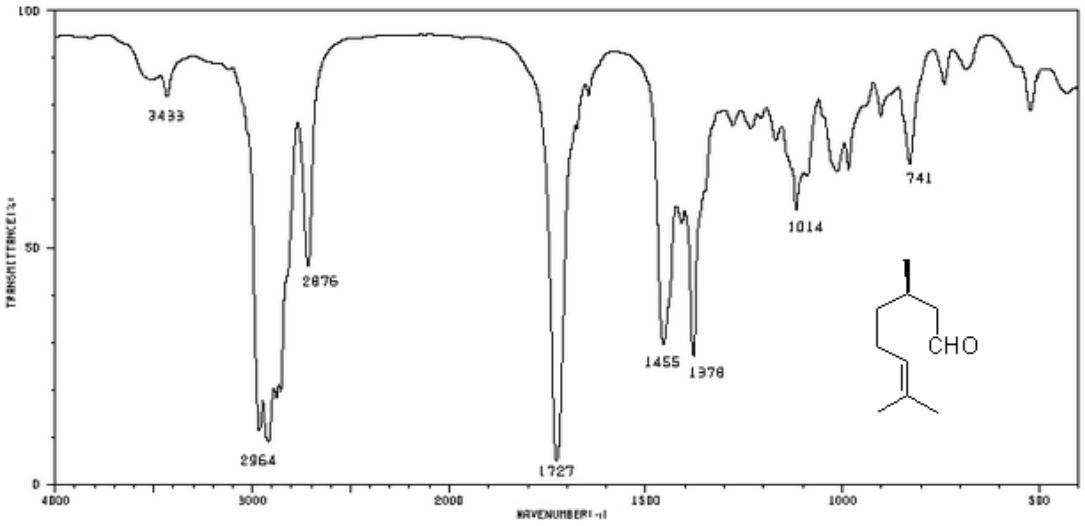
The obtained reaction mixture contains the Diels–Alder adduct and the ene-product (8:1) as a yellow oil. Leave the mixture in a fridge at 4 °C. After one week, wash the yellow crystals with petroleum ether. Weight the product (3*R*,4a*R*,10a*R*)-3,7,7,10,10-penthamethyl-5-oxo-6,8,9-trioxa-1,2,3,4,4a,5,6,7,8,9,10,10a-dodekahydrophenantren), calculate the yield, and characterize by m.p. (lit. m.p. 86 °C), TLC, IR and GC-MS.
The pure Diels–Alder adduct can be obtained by crystallization of the crude reaction product from diethyl ether/*n*-hexane (1:1): white needles, m.p. 104–106°C and $[\alpha]_D$ = 34.7 (c 0.7 $CHCl_3$).

Thin layer chromatography (TLC):

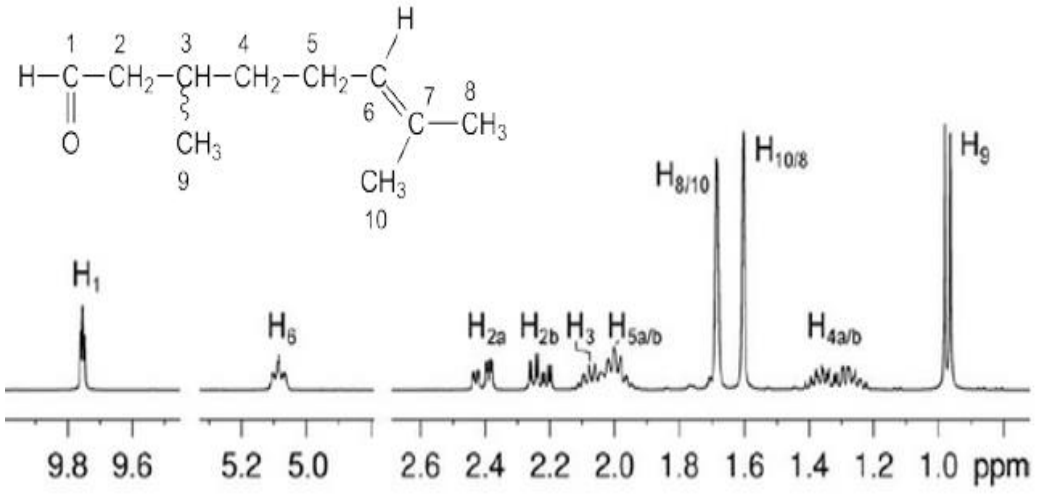
SiO_2 plate develop with CH_2Cl_2 and check under UV light. If the spots are visible in the UV light, mark them in a pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

SPECTRA

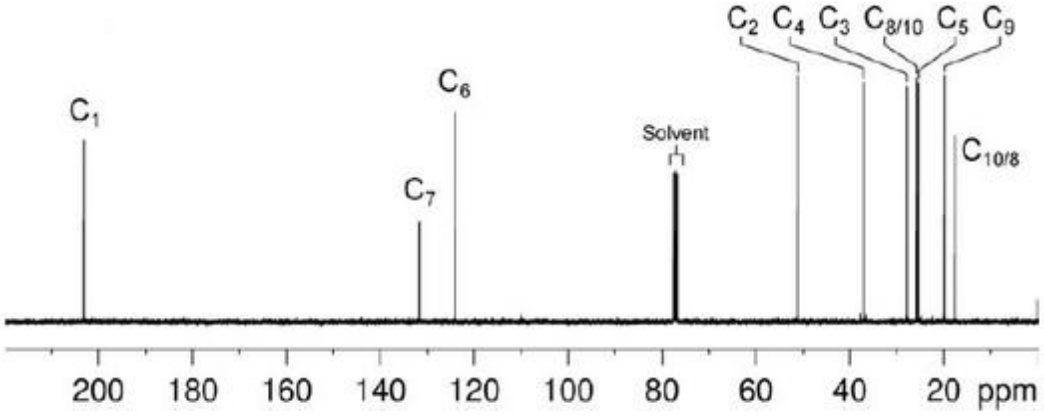
a) FT-IR spectrum of citronellal in KBr.



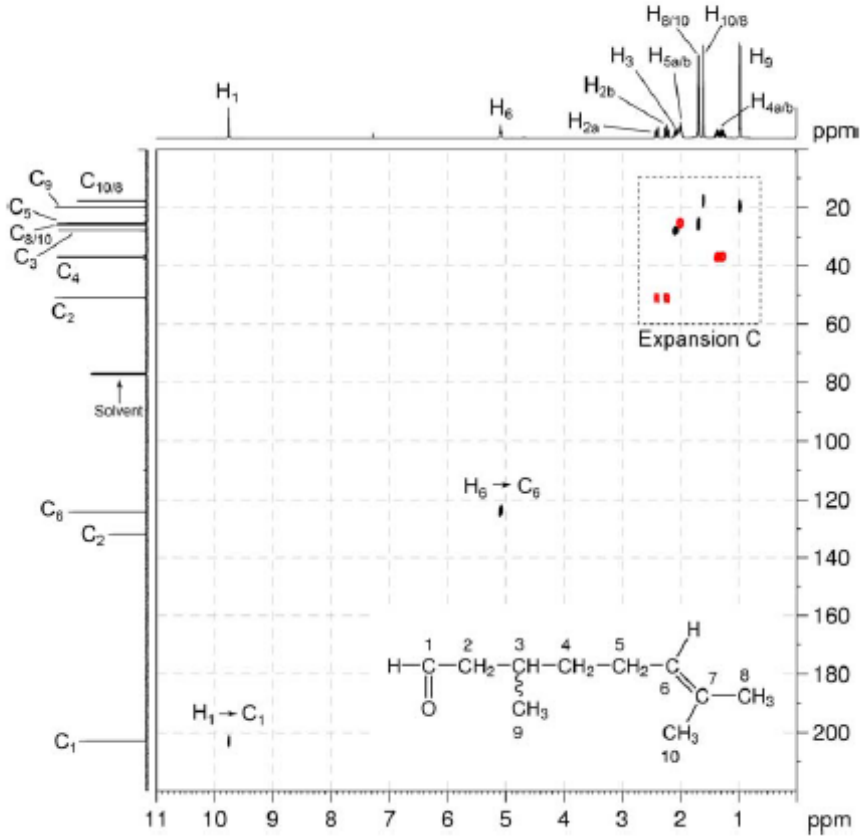
b) ^1H NMR spectra of citronellal (CDCl3, 400 MHz).



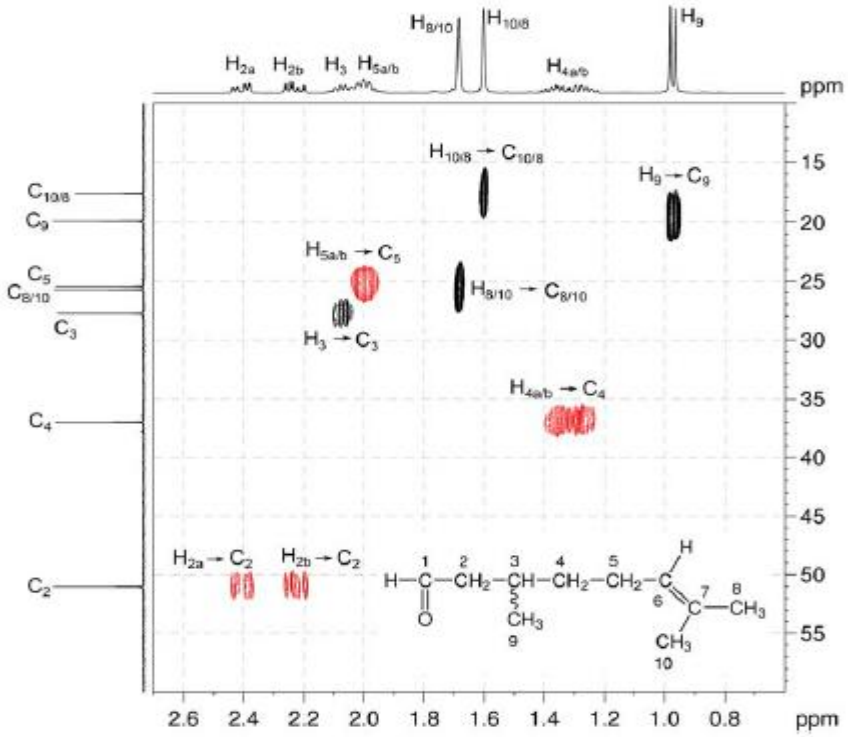
c) ^{13}C NMR spectra of citronellal (CDCl3, 400 MHz).



$^{1}H–^{13}C$ me-HSQC spectrum of citronellal (CDCl3, 400 MHz)



^{1}H–^{13}C me-HSQC spectrum of citronellal – expansion C

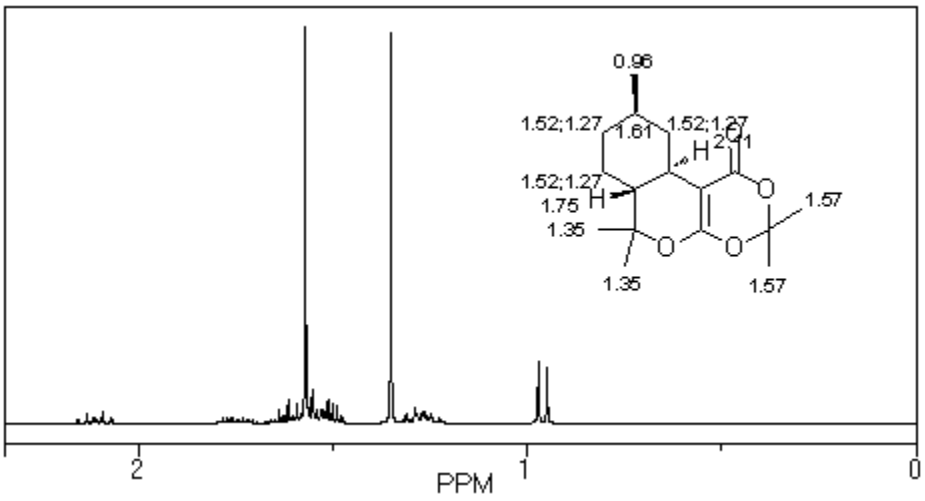


https://orgspectroscopyint.blogspot.com/2016/03/citronellal.html

d) FT IR of Diels-Alder product (KBr):

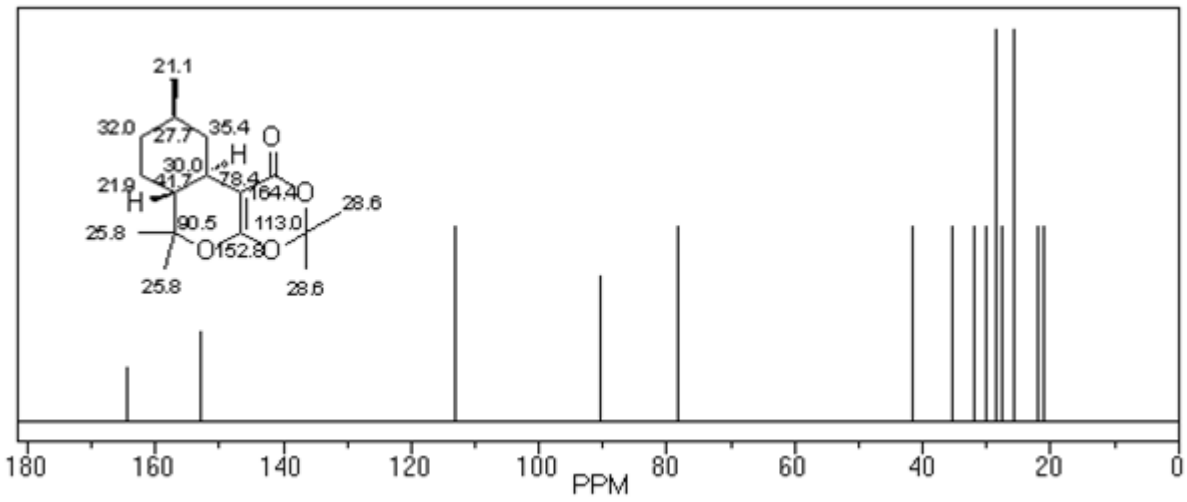
2950, 2930, 2860 (C-H), 1715 (C=O), 1615 (C=C), 1400, 1265 cm^{-1}.

e) ^{1}H NMR of Diels-Alder product - ChemDraw estimation.



^{1}H NMR of Diels-Alder product ($CDCl_3$) – experimental data δ: 0.40 (m, 1H, 4 β-H), 0.7–2.5 (m, 7H, CH + CH_2), 0.90 (d, 3H, *J* = 7, CH_3), 1.23, 1.43, 1.70, 1.73 (s, 3H, CH_3), 2.75 (dt, 1H, *J*1 = 12, *J*2 = 2, 4-H) ppm.

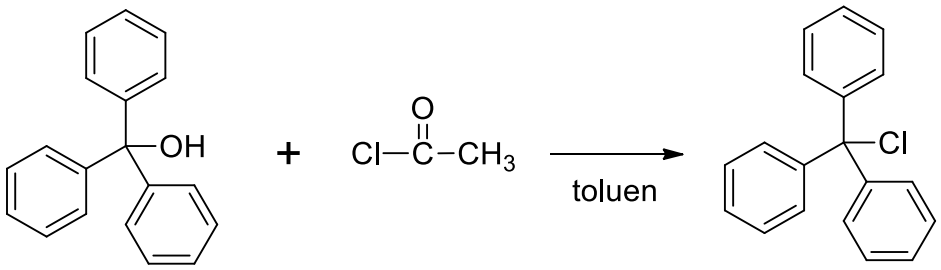
f) ^{13}C NMR spectra of Diels-Alder product – ChemDraw estimation.



References

https://orgspectroscopyint.blogspot.com/2016/03/citronellal.html

11. TRIPHENYLCHLOROMETHAN



Reagents:

triphenylmethanol	2,00 g
acetyl chloride	1.5 ml (excess)
toluene	8 ml

Instrumentation and glassware:

two-necked round-bottom flask 100 mL
condenser
drying tube
magnetic stirrer with heating
stirring bar
oil bath
thermometer
ice bath
filtering flask with Büchner funnel

To two-necked round-bottom flask (100 mL) equipped with condenser with a calcium-sulfate-filled drying tube and a magnetic stirring bar, place 2.0 g triphenylmethanol and 8 ml toluene. The second neck is covered with septum. The mixture is heated on an oil bath up to 80 ^{o}C; when it is hot, 0.5 ml of acetyl chloride is added through the septum (use a syringe with needle).

Heating is continued while the mixture is shaken vigorously. In about 5 minutes, all the solid triphenylcarbinol disappears. After 10 minutes, an additional 1.0 mL of acetyl chloride is slowly added in small portions. The solution is then refluxed for additional 30 min.

Then, the reaction mixture is cooled in an ice bath, and during this operation 20 mL of cold petroleum ether is added through the top of the condenser (Note 2). The triphenylchloromethane separates in sugar-like crystals. The mixture is cooled in an ice bath for 2 hours, and the product is filtered (Note 3) and washed with 20 mL of petroleum ether (Note 4). If the product does not precipitate, concentrate the mixture on rotary evaporator and to the slurry mixture add 10 mL of petroleum ether.

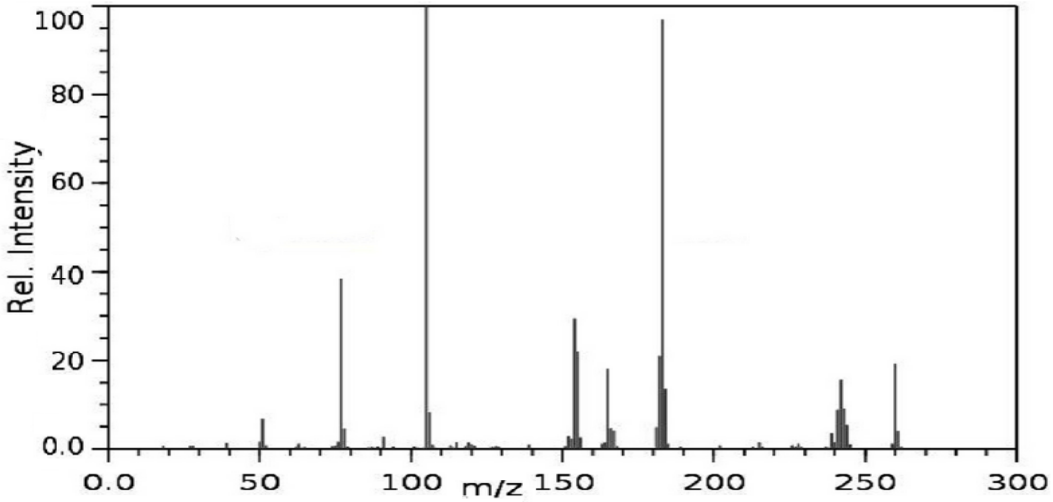
The colourless solid, after drying leave in a desiccator, m.p. 111–112° with slight previous softening (Notes 5 and 6). Yield 79–83%.

Notes:

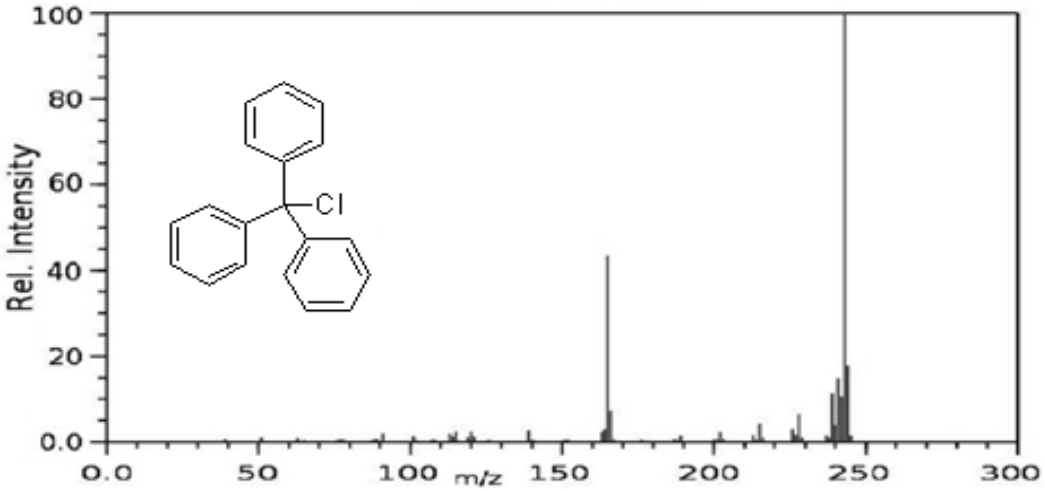
(1) It is best to carry out the reaction under a fume hood.
(2) Petroleum ether having a boiling point of 30–60° should be used because it is easily removed from the product.
(3) The filtration should be rapid. Triphenylchloromethane is hydrolysed by moisture in the air.
(4) The final product is perfectly colourless and should have no sharp odour.
(5) It may recrystallize by dissolving it in 5 mL of hot toluene and cooling the solution after diluting it with 5 mL of petroleum ether.
(6) If the product is kept in a bottle, the stopper should be coated with paraffin in order to keep out the moisture of the air that causes decomposition of the product.

SPECTRA

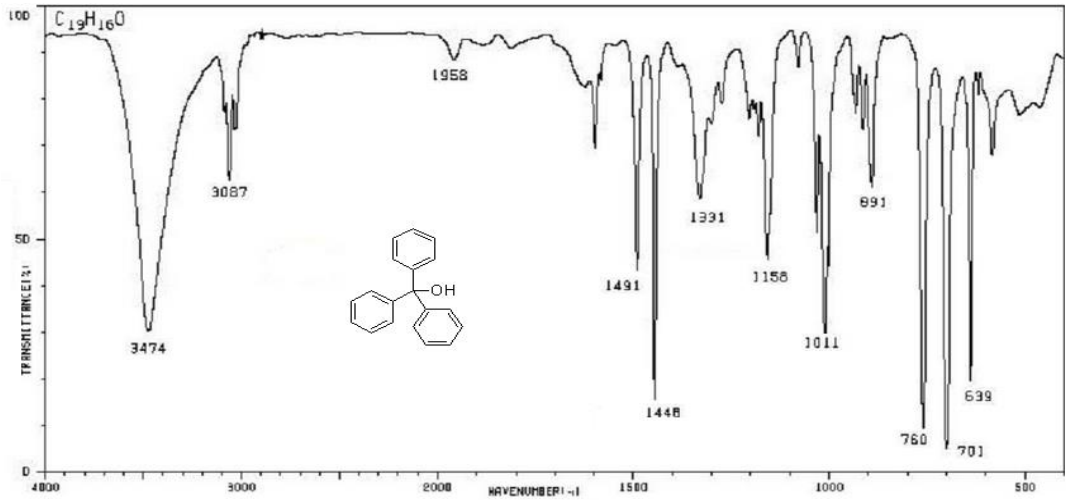
a) EI-MS spectrum of triphenylmethanol



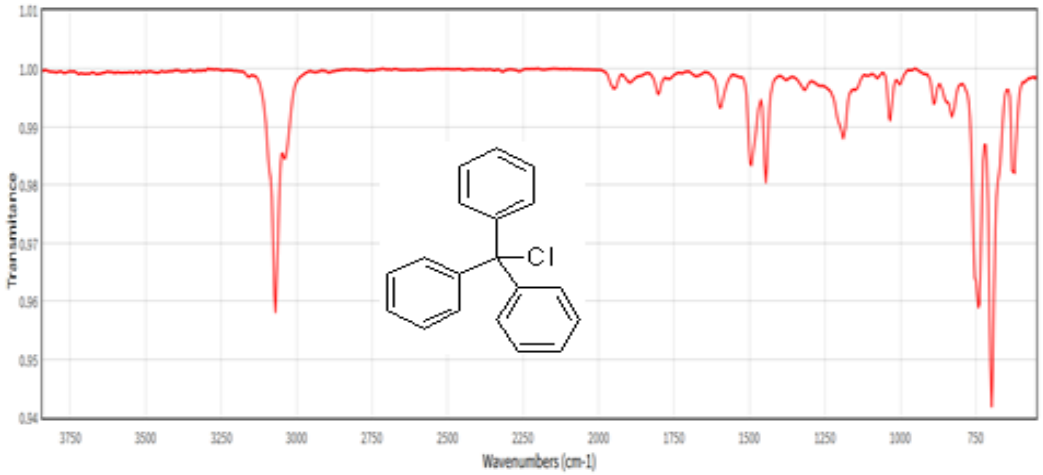
b) EI-MS spectrum of triphenylchloromethane



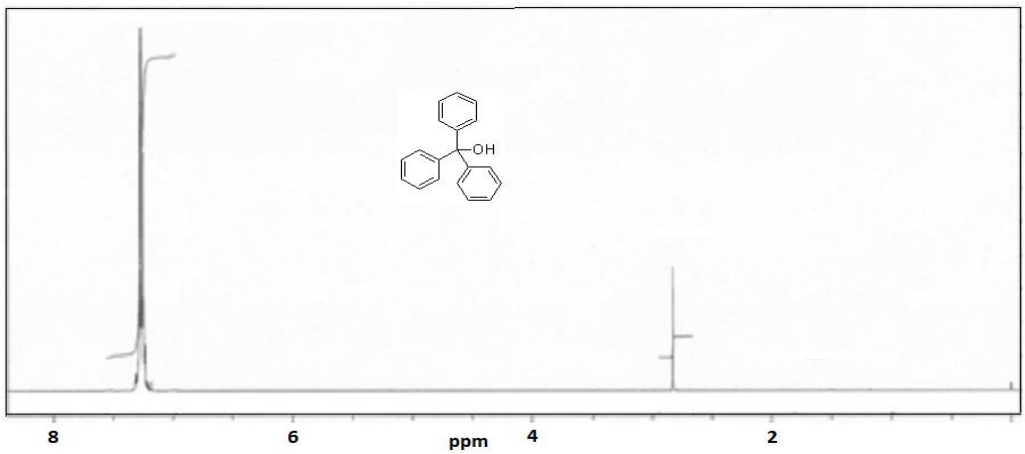
c) FT-IR spectrum of triphenylmethanol (KBr disc)



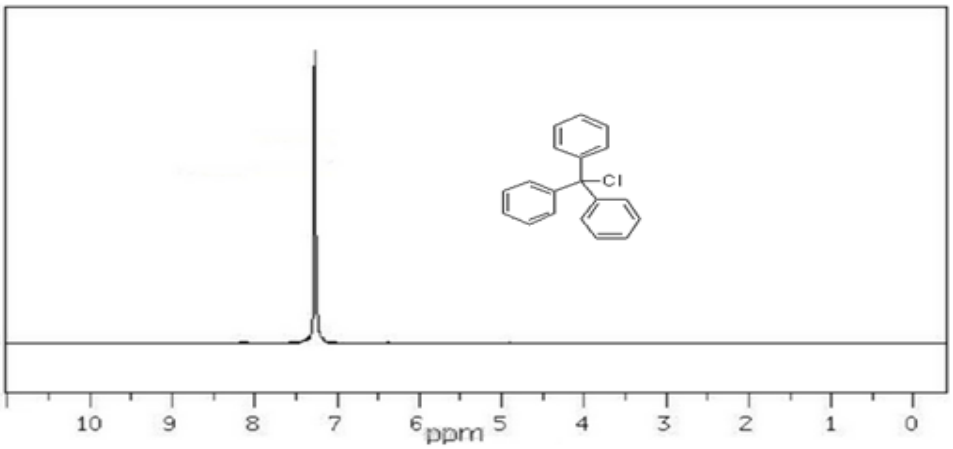
d) FT-IR spectrum of triphenylchloromethane



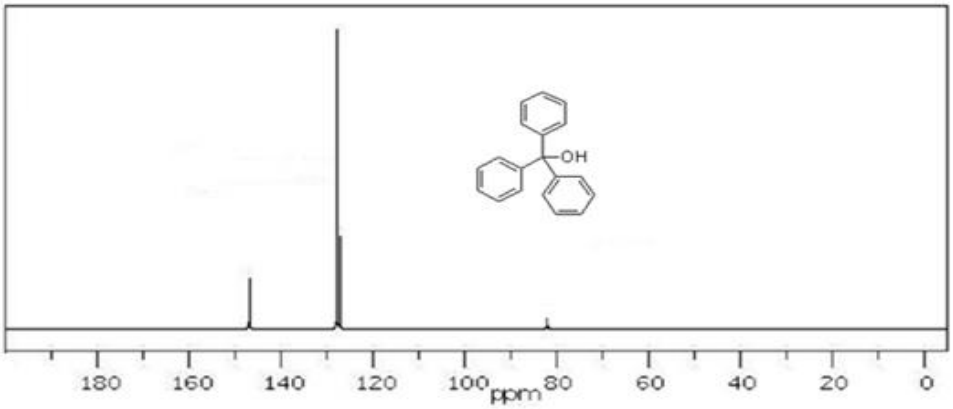
e) ^{1}H NMR spectrum of triphenylmethanol in $CDCl_3$



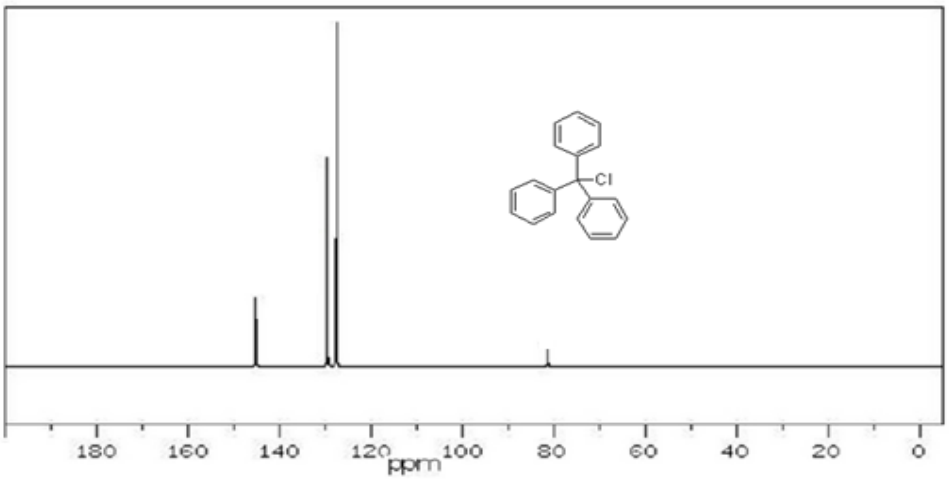
f) ^{1}H NMR spectrum of triphenylchloromethane in $CDCl_3$



g) ^{13}C NMR spectrum of triphenylmethanol in $CDCl_3$



h) ^{13}C NMR spectrum of triphenylchloromethane in $CDCl_3$

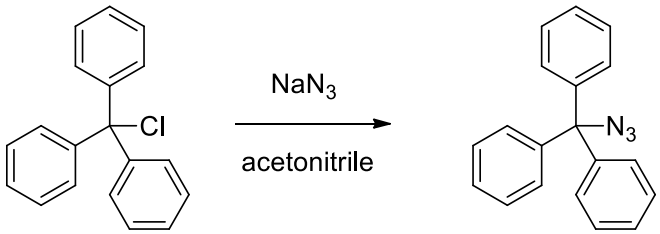


References

Bachmann W. E.: Triphenylchloromethane. *Org. Synth.*, *23*, 1943, 100 (DOI: 10.15227/orgsyn.023.0100)

https://www.guidechem.com/

12.TRIPHENYLMETHYL AZIDE (TRITYL AZIDE)



Reagents:

trityl chloride	1.56 g
sodium azide	0.55g
acetonitrile	15 mL
CH_2Cl_2	40 mL
n-hexane	50 mL

Instrumentation and glassware:

round-bottom flask 50 mL
condenser
magnetic stirrer with heating
stirring bar
oil bath
thermometer
ice bath
filtering flask with Büchner funnel

Note:
Sodium azide is potentially explosive and it is a strong poison. Work under a fume hood.
It must not be allowed to come into contact with acids.

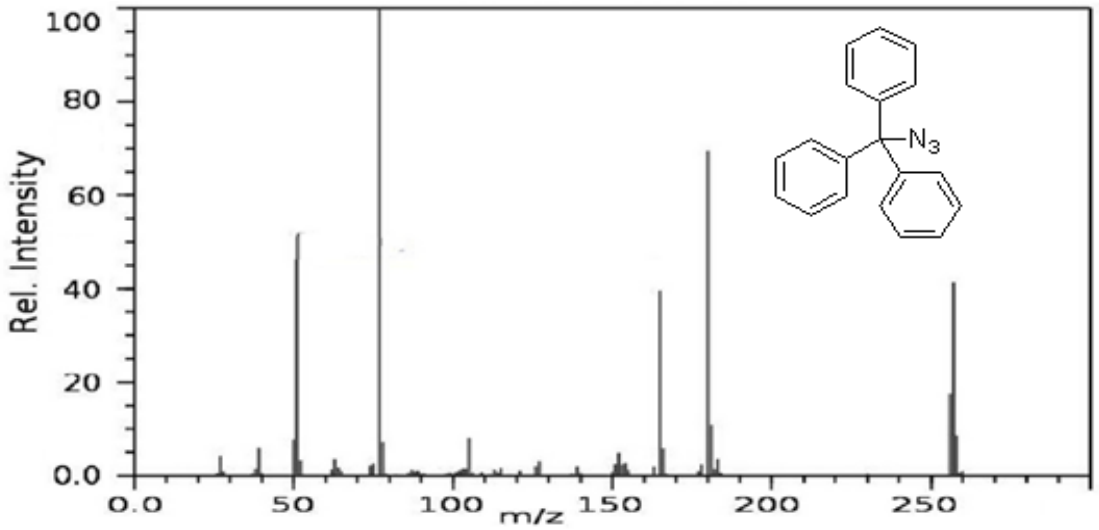
To a round-bottom flask 50 mL equipped with condenser, with drying tube filled with $CaCl_2$ and a magnetic stirring bar, place trityl chloride (1.56 g), 15 mL acetonitrile and sodium azide 0.55 g. The mixture is heated on an oil bath up to 80 ^oC for 3 hours.

Then, the solution is cooled to room temperature and the solid is separate on Büchner funnel. The solid on funnel wash twice with CH_2Cl_2 (2 x 10 mL). Combine together the filtrates and concentrate using rotary evaporator.

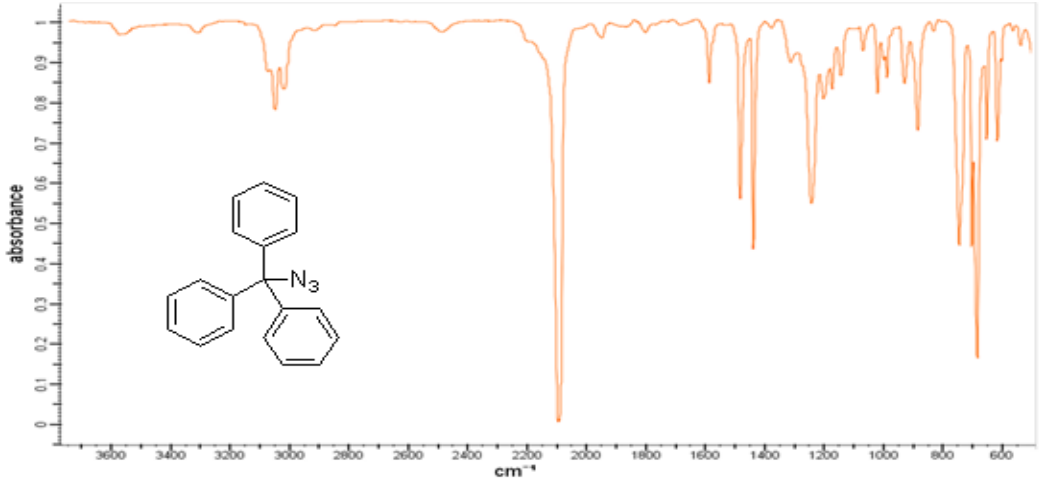
The residue dissolve in 5 mL of *n*-hexane and filter through a small column filled with silica gel (**Fig**. **1**, chapter 2). Wash the column with *n*-hexane (20 mL), then with mixture of *n*-hexane-CH_2Cl_2 (1:1, 10 mL:10 mL). Collect the filtrate directly in a round-bottom flask. This operation is filtration (not column chromatography), which aims to stop the remaining inorganic salts on silica gel. For this reason, the filtrate is directly collected in a round-bottom flask. Evaporate the solvents and the crude product recrystallize from *n*-hexane. Yield 97%

SPECTRA

a) EI-MS spectrum of trityl azide



b) FT-IR spectrum of trityl azide



c) **^{1}H NMR**

(d_6-DMSO, 400MHz): 7.41 (m, 9H), 7.26 (m, 6H) ppm

d) **^{13}C NMR**

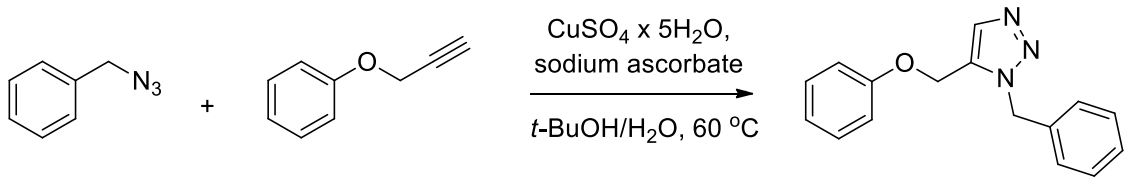
(d_6-DMSO, 100MHz): 142.5, 128.4, 127.9, 77.0 ppm

References

https://www.guidechem.com/

https://spectrabase.com/

13.1-BENZYL-4-(PHENOXYMETHYL)TRIAZOLE



Reagents:

benzyl azide	133 mg
phenyl propargyl ether	130 µL
sodium ascorbate	19,8 mg
$CuSO_4$ x $5H_2O$	50 µL

Instrumentation and glassware:

20 mL screw-top scintillation vial
stirring bar
filtering flask with Büchner funnel

133 mg of benzyl azide and 130 µL of phenyl propargyl ether are stirred in 2–3 ml of *tert*-BuOH/water (1:1) solution in a 20 mL screw-top scintillation vial. 19,8 mg (10 mol%) sodium ascorbate and 50 µL (5 mol%) of 1.0 M aq. $CuSO_4$ x $5H_2O$ are added sequentially and the mixture is stirred at 60 °C for 2 hours until completion, monitored by TLC (*n*-hexane/ethyl acetate 2:1) – **Figure 4**. Reaction mixture is then diluted with 10 mL ice water, followed by the addition of 2 mL of 10 % aqueous ammonia. After stirring for another 5 minutes, the solid precipitate is collected with a Büchner filter and air-dried overnight (lit. m.p. 112–114 °C).

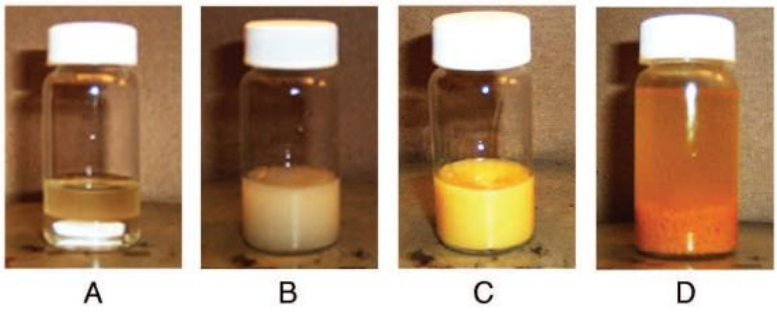


Figure 4. Reaction progress of benzyl azide and phenyl propargyl ether: (A) before addition of $CuSO_4$, (B) 30 minutes, (C) 120 minutes, and (D) after dilution with water and addition of aqueous ammonia (source: W.D. Sharpless, P. Wu, T.V. Hansen, J.G. Lindberg, J. Chem. Educ. 82 (2005) 1833–1836).

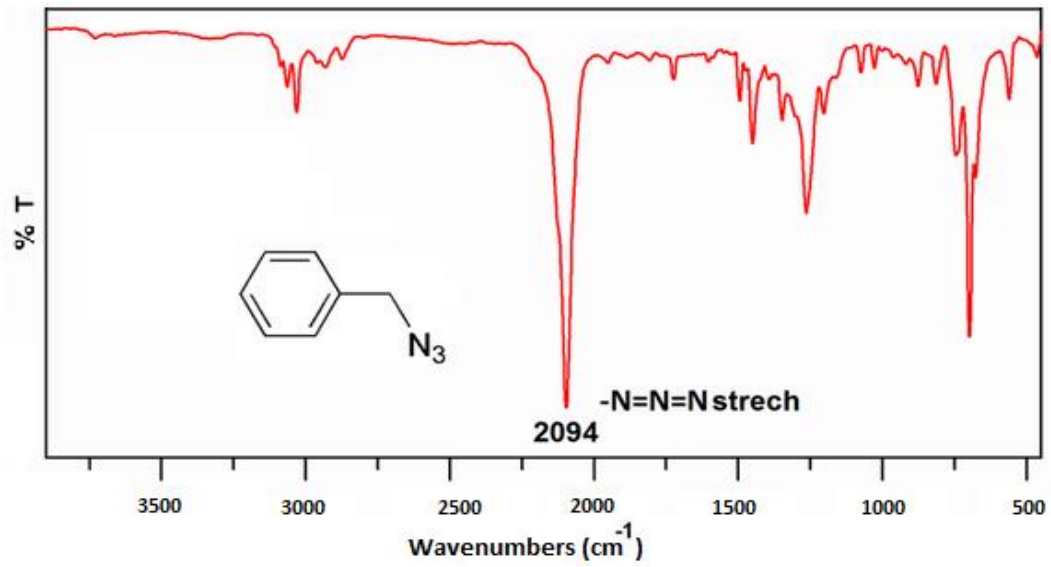
Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with *n*-hexane/ethyl acetate (2:1). Remove the plate and allow the solvent to evaporate and inspect under UV light.

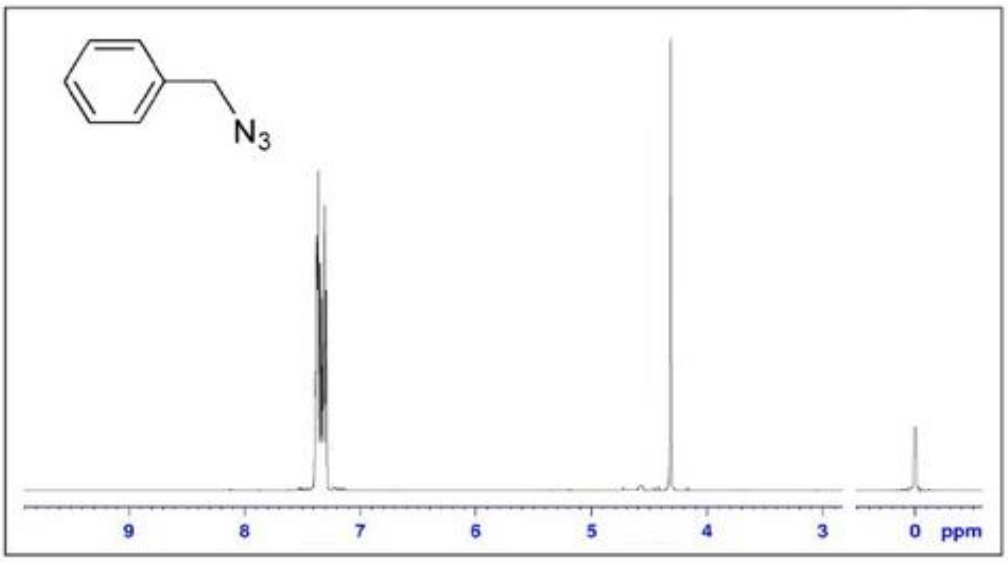
Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

SPECTRA

a) FT-IR spectrum of benzyl azide.



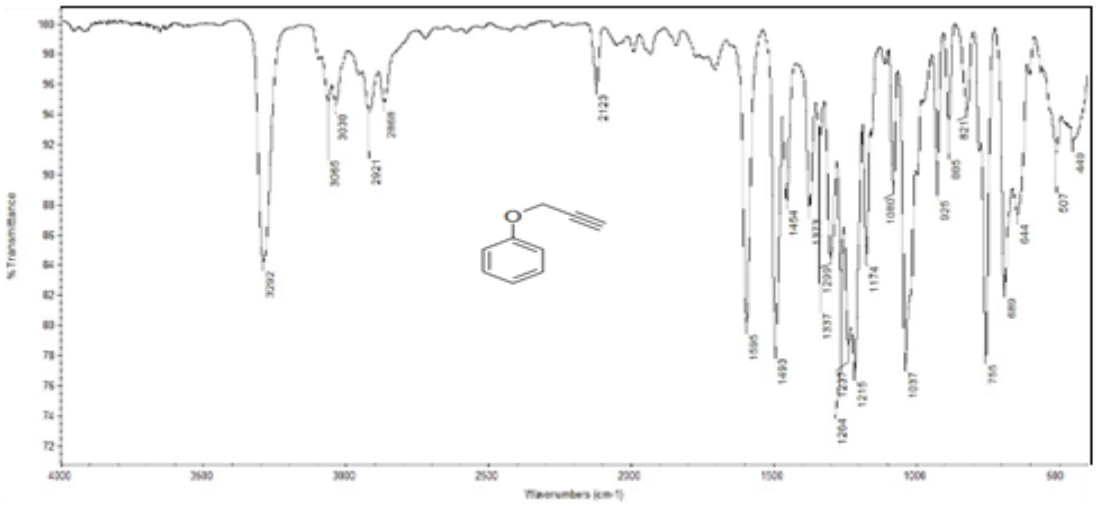
b) ^{1}H NMR spectrum of benzyl azide.



^{1}H-NMR (300 MHz, CDCl3): δ 4.3 (s, 2H), 7.27-7.39 (m, 5H).

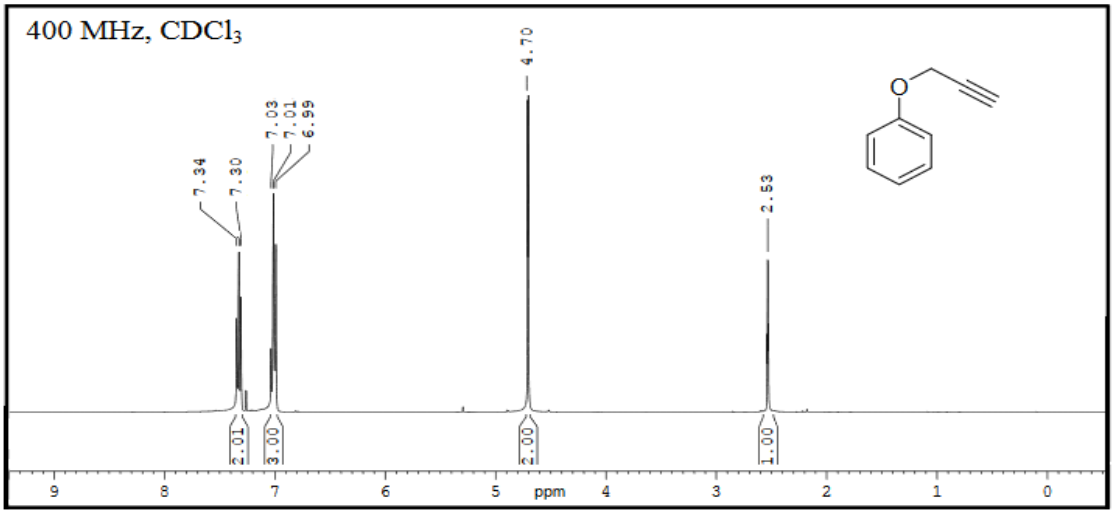
c) **^{13}C-NMR** (75 MHz, CDCl3): δ 54.8, 128.2, 128.3, 128.8, 135.4.

d) FT-IR spectrum of phenyl propargyl ether

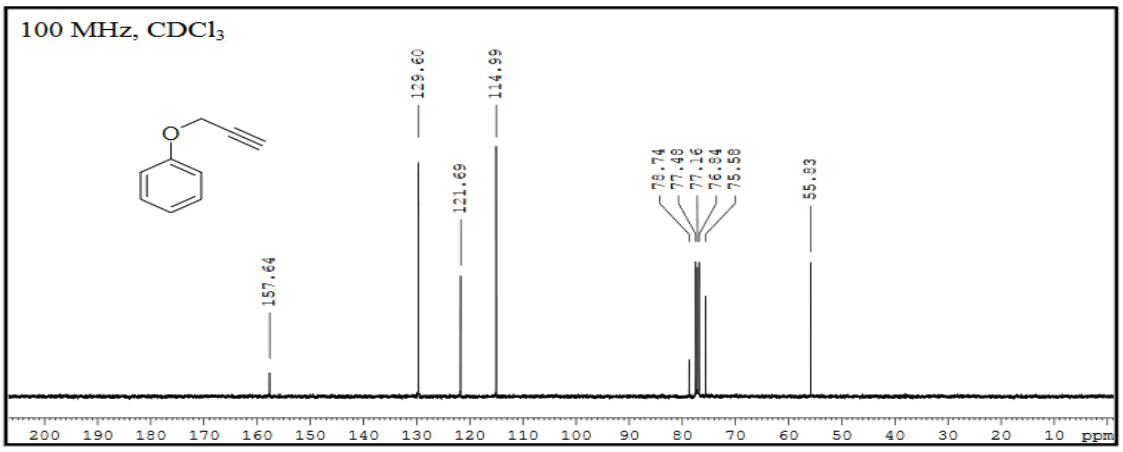


https://pdfs.semanticscholar.org/8065/5d9b7f48e1b55f34ae6bf58b285079f778a8.pdf

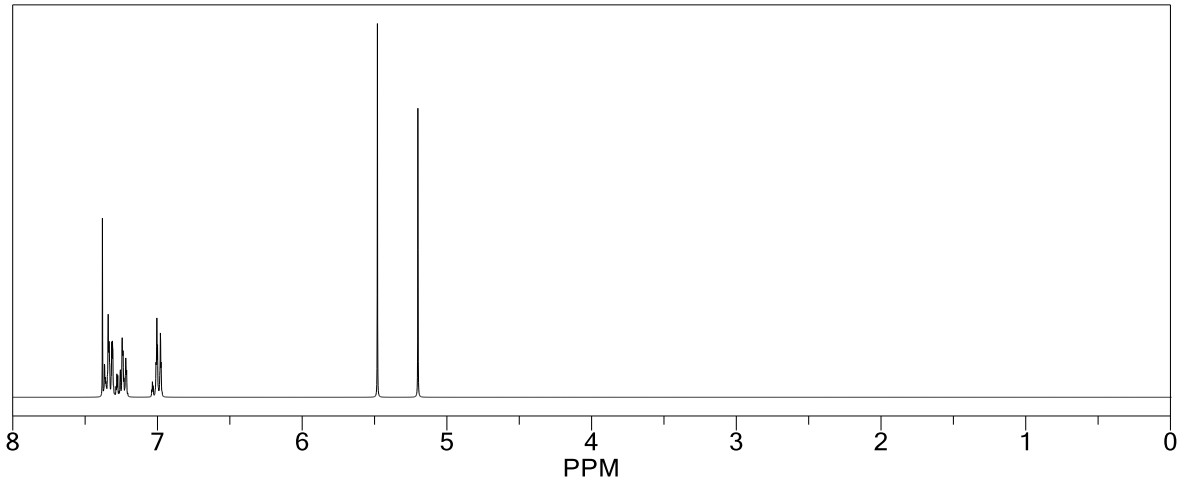
e) ^{1}H NMR spectrum of phenyl propargyl ether ($CDCl_3$, 400 MHz).



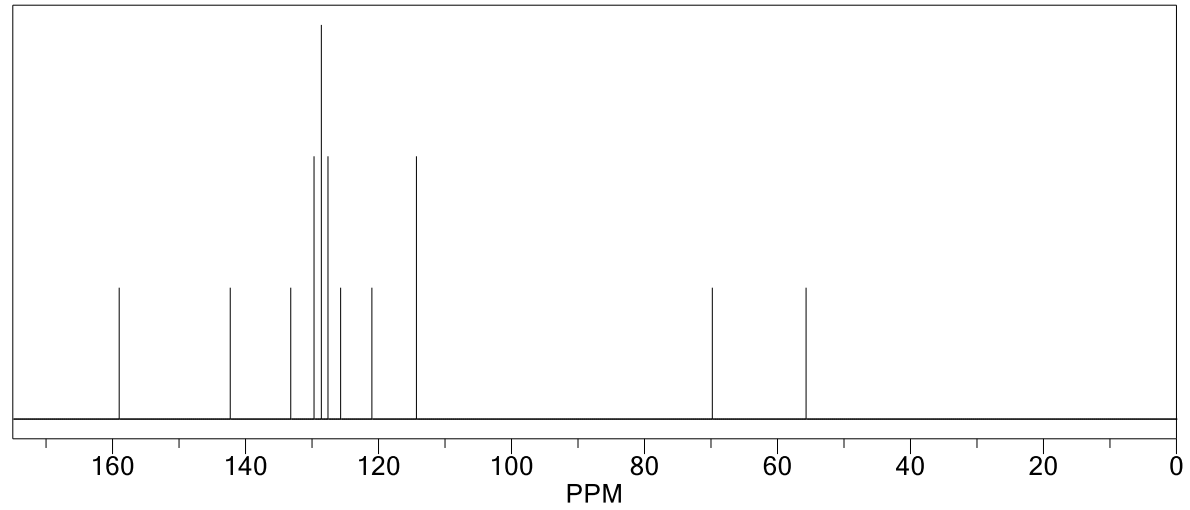
f) ^{13}C NMR spectrum of phenyl propargyl ether ($CDCl_3$, 100 MHz).



g) ^{1}H NMR spectrum of 1-benzyl-4-(phenoxymethyl)triazole (ChemNMR ^{1}H Estimation)



h) ^{13}C NMR spectrum of 1-benzyl-4-(phenoxymethyl)triazole (ChemNMR ^{13}C Estimation)



References

Sharpless W.D., Wu P., Hansen T.V., Lindberg J.G.: Just Click It: Undergraduate Procedures for the Copper(I)-Catalyzed Formation of 1,2,3-Triazoles from Azides and Terminal Acetylenes. *J. Chem. Educ.* 82, **2005**, 1833–1836.

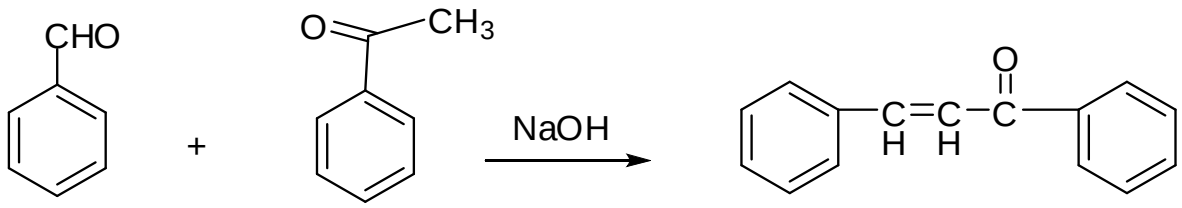
Jain S., Kumar P., Joshi Ch., Srivastava A.K., Gupta P., Boukherroub R.: Visible Light Assisted Photocatalytic [3+ 2] Azide–Alkyne "Click" Reaction for the Synthesis of 1, 4-Substituted 1, 2, 3-Triazoles Using a Novel Bimetallic Ru–Mn Complex. Supporting information ACS *Sus. Chem. Eng.* 2016, 4 (1), pp 69–75.

https://spectrabase.com/spectrum/C1TK3Ezcc3H?a=SPECTRUM_C1TK3Ezcc3H

Surya Prakash Rao H., Kamalraj M., Prabakaran M.: Synthesis and physico-chemical properties of H-cardanol triazole zinc porphyrin conjugate. *RSC Advances* 9 (2019) 4499-4506 Supporting information. DOI: 10.1039/C8RA09998G.

https://pdfs.semanticscholar.org/8065/5d9b7f48e1b55f34ae6bf58b285079f778a8.pdf

14. CHALCONE (BENZYLIDENEACETOPHENONE)



Reagents:		**Instrumentation and glassware:**
NaOH	2.2 g	two-necked round-bottom flask 100 mL
ethanol	13 mL	condenser
acetophenone	5 mL	dropping funnel (50 mL)
benzaldehyde	4.4 mL	magnetic stirrer
		thermometer
		filtering flask with Büchner funnel
		water bath

WARNING! Work under fume hood! Wear the gloves!

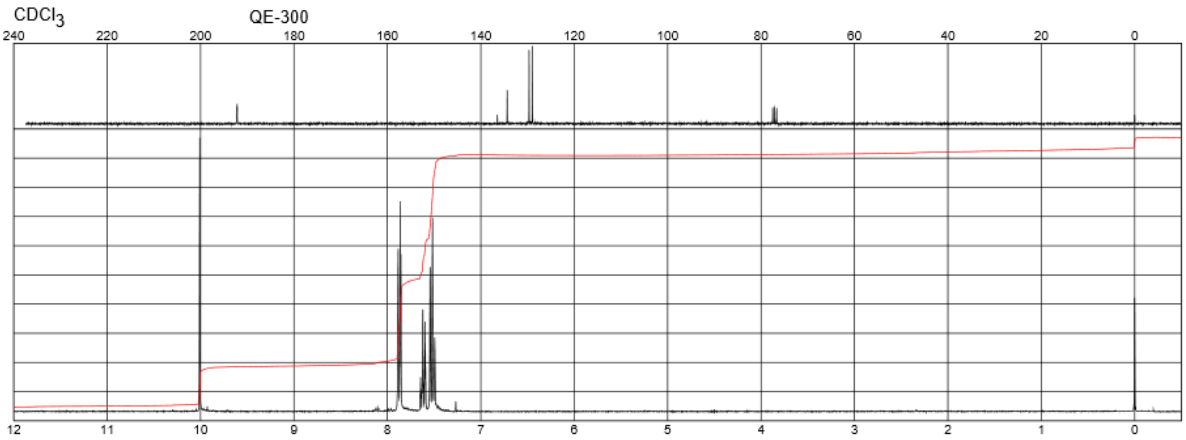
To 100 mL two-necked round-bottom flask with magnetic stirrer and condenser, place solution of 2.2 g NaOH in 20 mL of distilled water and 12.25 mL of ethanol. Place flask in the bath with crushed ice and add dropwise by dropping funnel 5 mL of acetophenone, and then 4.4 mL of benzaldehyde. Keep the temperature of reaction mixture at about 25 ^{o}C (the proper range of temperature of reaction mixture is 15–30^{o}C), stir vigorously till the forming product prevents stirring (usually after 2–3 hours). Remove magnetic stirrer and leave the reaction overnight in a fridge. Filter the obtaining product on a Büchner funnel and wash the product with cold water until pH 7. Once achieve this, rinse it with ethanol (8 mL). Recrystallize the crude product from ethanol (ca. 10 mL) and heat under reflux for 20 min. Allow the resulting mixture to crystallize in the refrigerator for one week. Weigh the product, calculate the yield of pure chalcone and measure the m.p. (lit. m.p. 56–57 ^{o}C).

Thin layer chromatography (TLC):

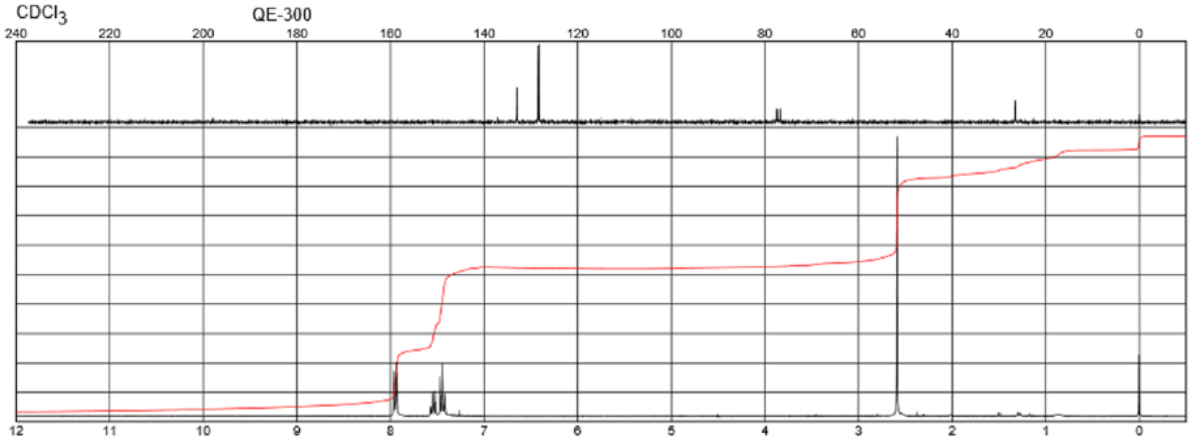
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with ethanol/CH_2Cl_2 (5:5). Remove the plate and allow the solvent to evaporate. The spot of the product is visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECRTA

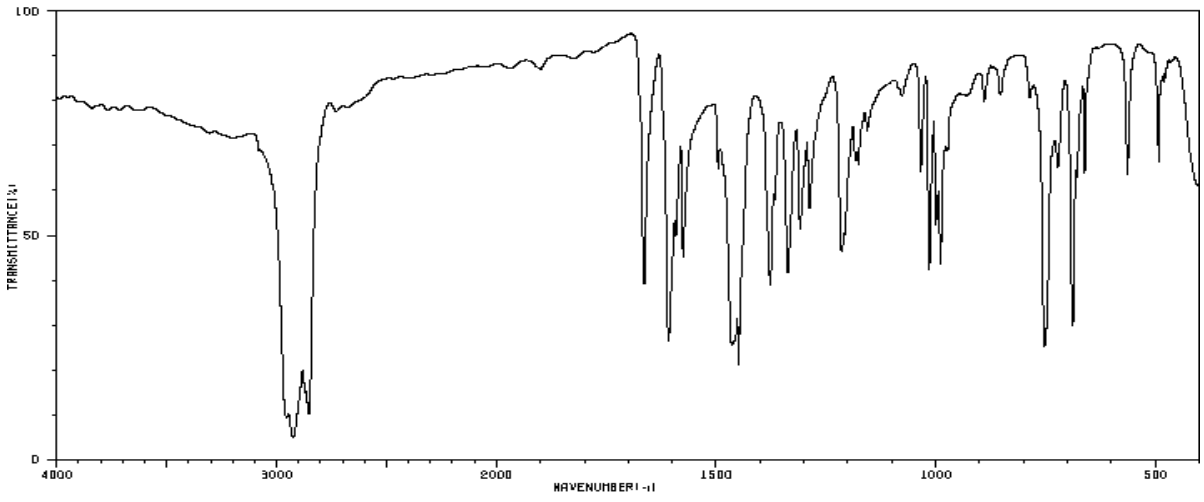
a) ^{1}H NMR and ^{13}C NMR spectra of benzaldehyde ($CDCl_3$, Sigma Aldrich).



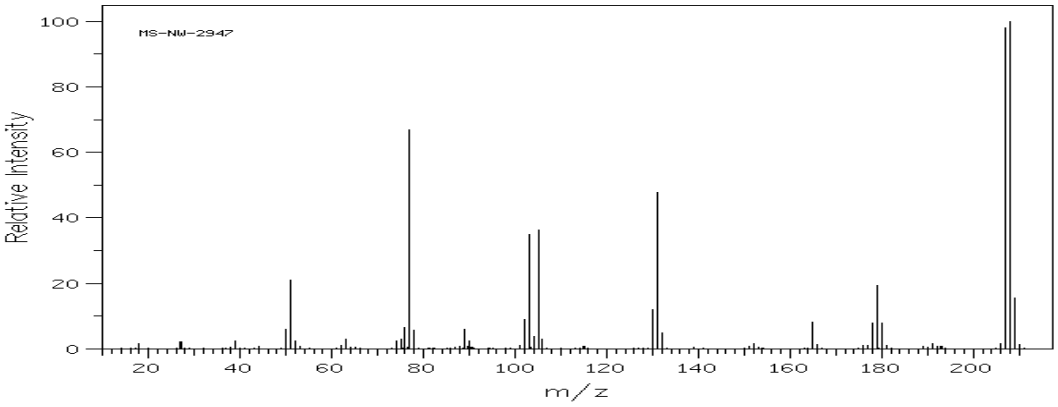
b) ^{1}H NMR and ^{13}C NMR spectra of acetophenone ($CDCl_3$, Sigma Aldrich).



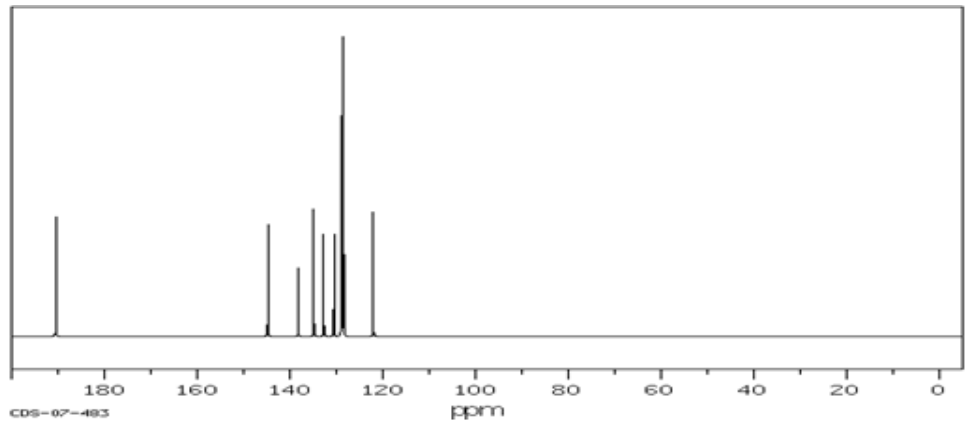
c) FT-IR spectrum of chalcone in nujol.



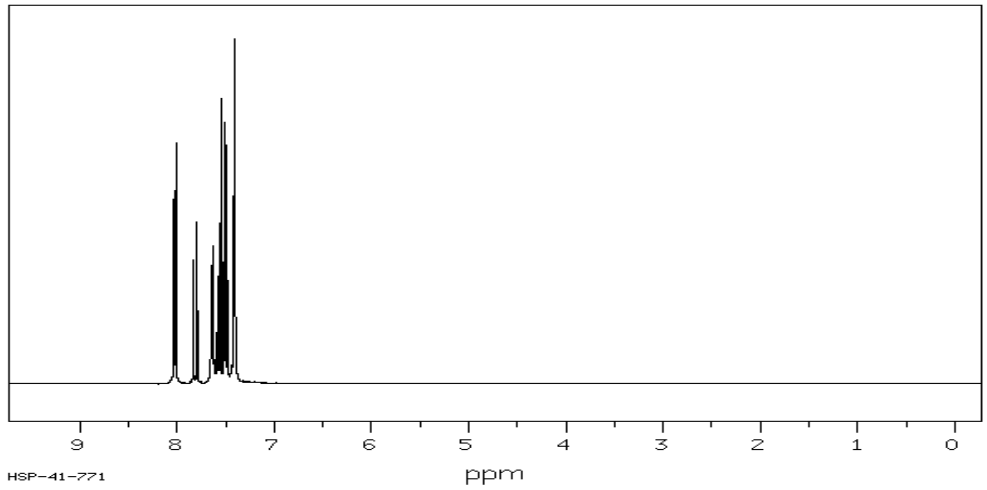
d) MS spectrum of chalcone.



e) ^{13}C NMR spectrum of chalcone in $CDCl_3$.



f) ^{1}H NMR spectrum of chalcone in $CDCl_3$.

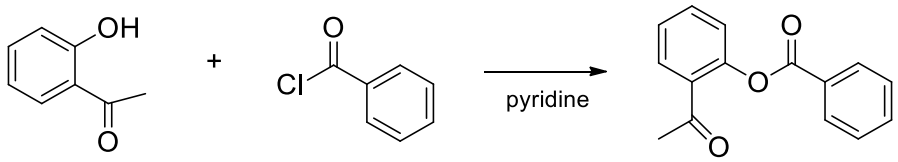


Rferences

Zhuang C., Zhang W., Sheng C., Zhang W., Xing C., Miao Z. **:** Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem. Rev. 117* (2017) 7762-7810.

15. FLAVONE (3-step synthesis)

STEP 1 2-BENZOILOXOACETOPHENONE



Reagents:		**Instrumentation and glassware:**
2-hydroxyacetophenone	3.4 g	conical flask with stopper 50 mL
benzoyl chloride	4 mL	beaker 250 mL
pyridine	5 mL	filtering flask with Büchner funnel
1.0 M HCl	120 mL	
methanol	15 mL	

Place 3.4 g 2-hydroxyacetophenone into conical flask (50 mL), add 4 mL benzoyl chloride and 5 mL anhydrous, freshly distilled pyridine, and close the flask with plastic (PE) stopper. **All operations should be done under efficiently working fume hood and with protecting gloves!** Flask should be shaken till its content is mixed. The temperature of reaction mixture will raise. After 20 min, carry the reaction mixture into a beaker with 120 mL of 1.0 M HCl with 50 g of crushed ice. Filter the product on Büchner funnel and wash with 5 mL of methanol cooled in ice bath, and then with 5 mL of distilled water. To recrystallize product dissolve it in methanol (6–8 mL), heat, and then cool down the mixture in ice bath and filter the product under reduced pressure. Weigh and calculate the yield.

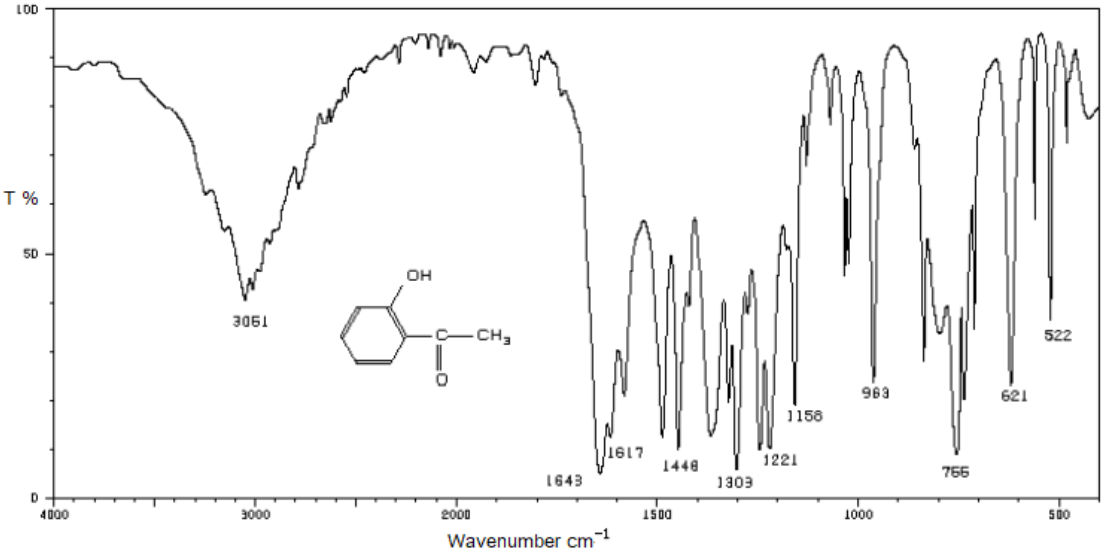
Measure melting point of 2-benzoiloxoacetophenone (lit. m.p. 87–88 ^{o}C).

Thin layer chromatography (TLC):

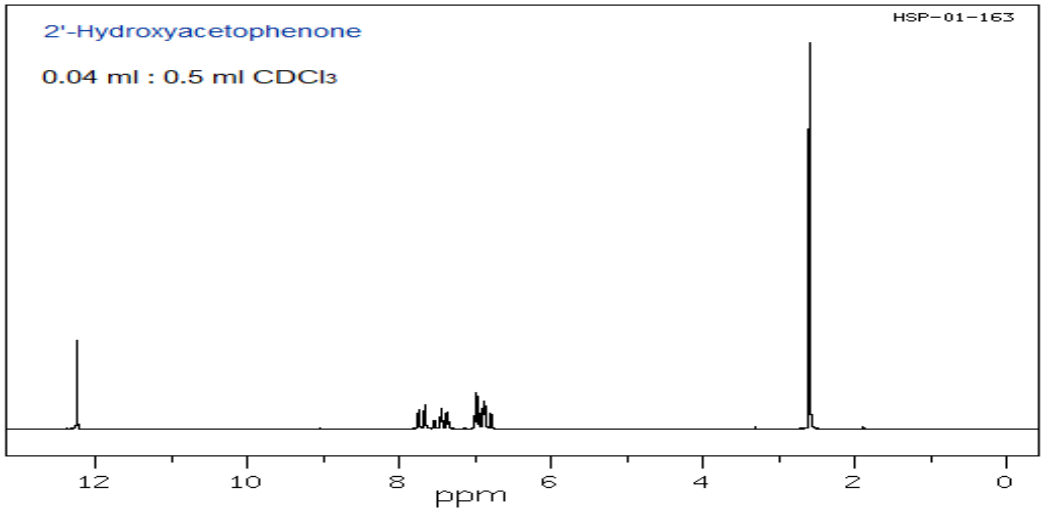
Apply the substrate and product (as a solution in chloroform) onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with *n*-hexane/acetone (2:8). Remove the plate and allow the solvent to evaporate. The spots of the compounds are visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

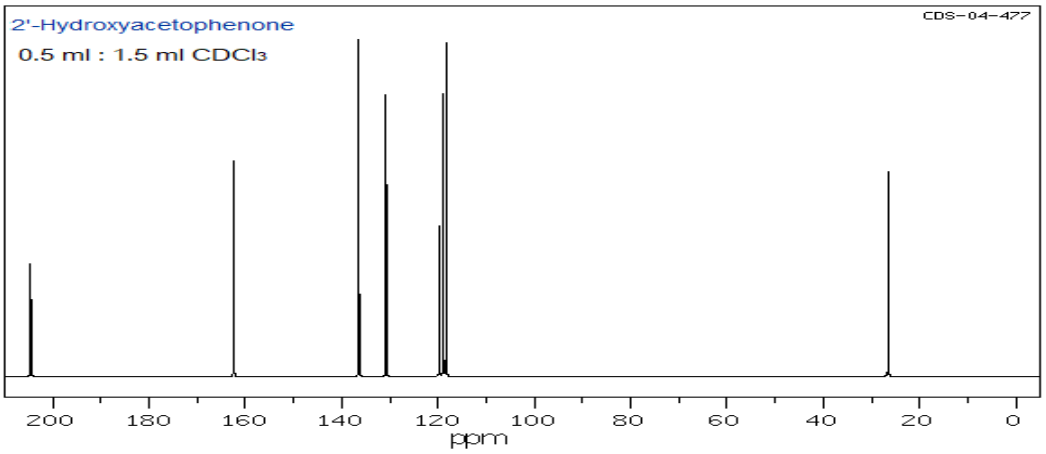
a) FT-IR spectrum of 2-hydroxyacetophenone.



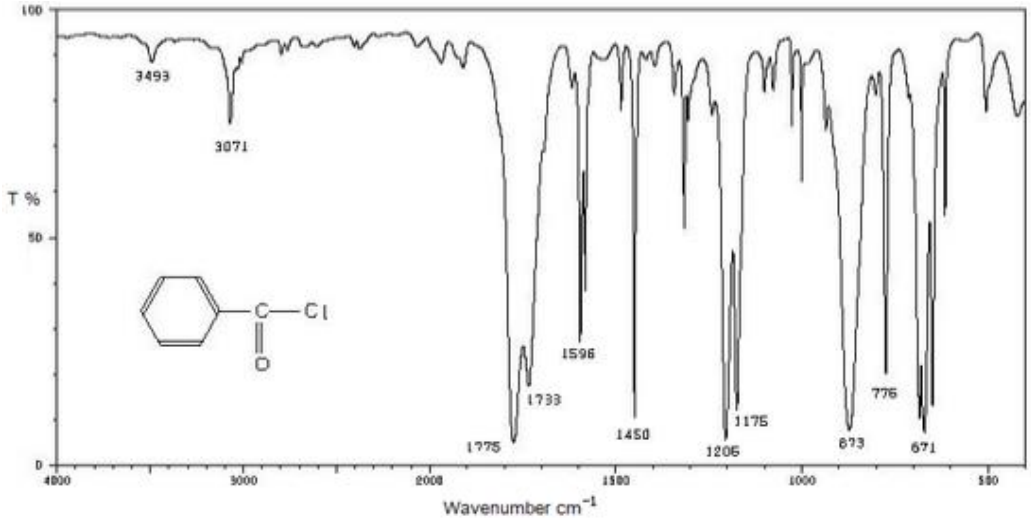
b) ^{1}H NMR spectrum of 2-hydroxyacetophenone in $CDCl_3$.



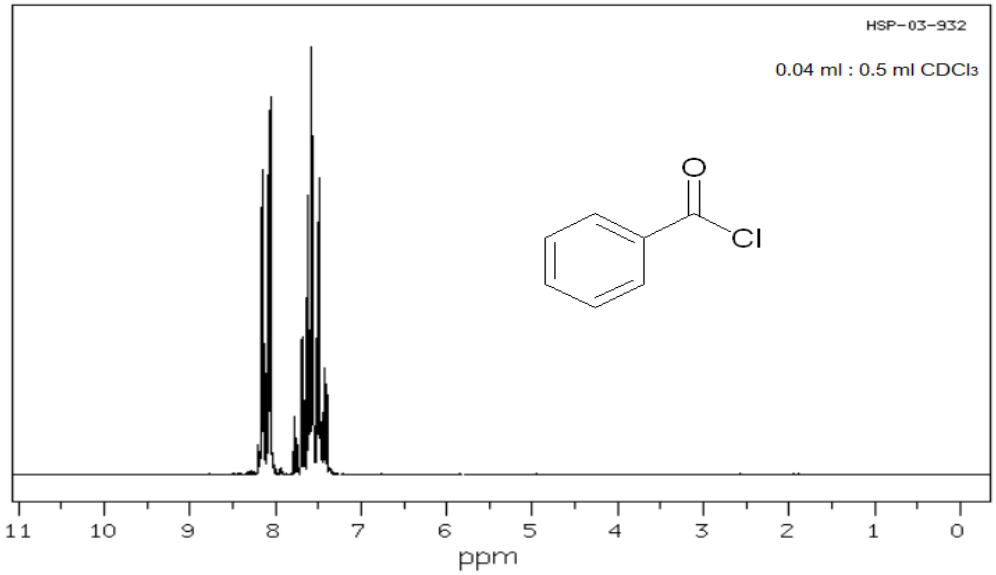
c) ^{13}C NMR spectra of 2-hydroxyacetophenone in $CDCl_3$.



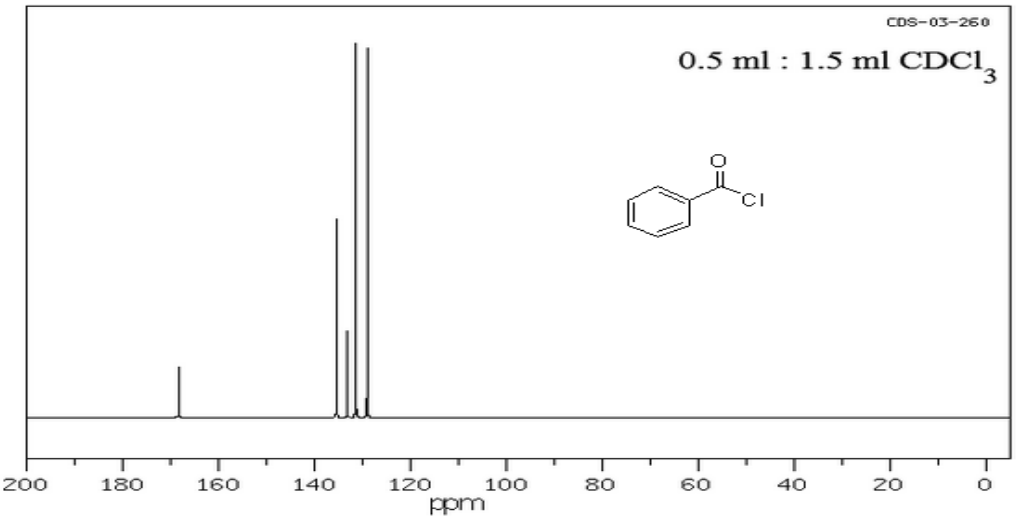
d) FT-IR spectrum of benzoyl chloride.



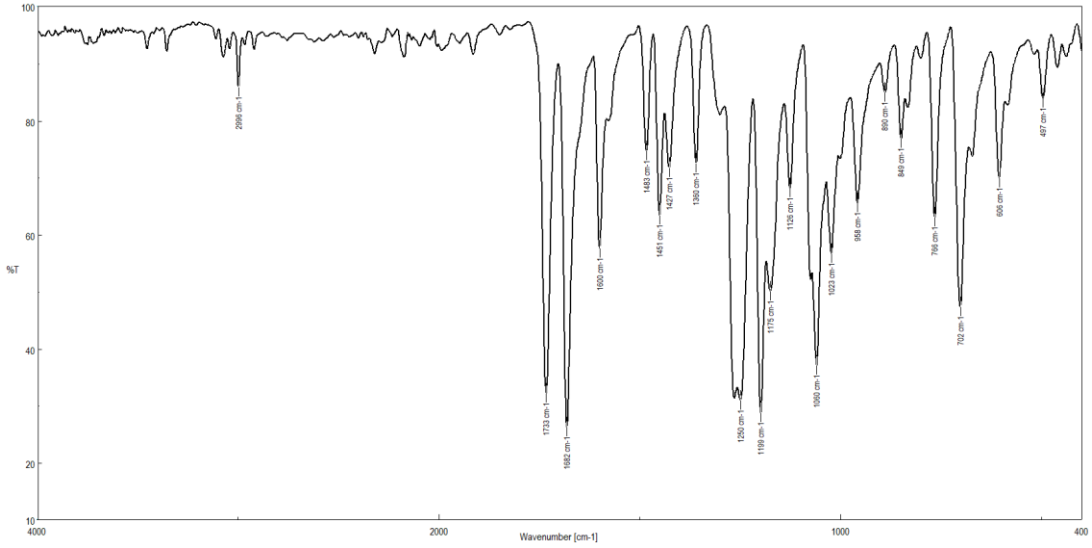
e) ^{1}H NMR spectrum of 2-hydroxyacetophenone in $CDCl_3$.



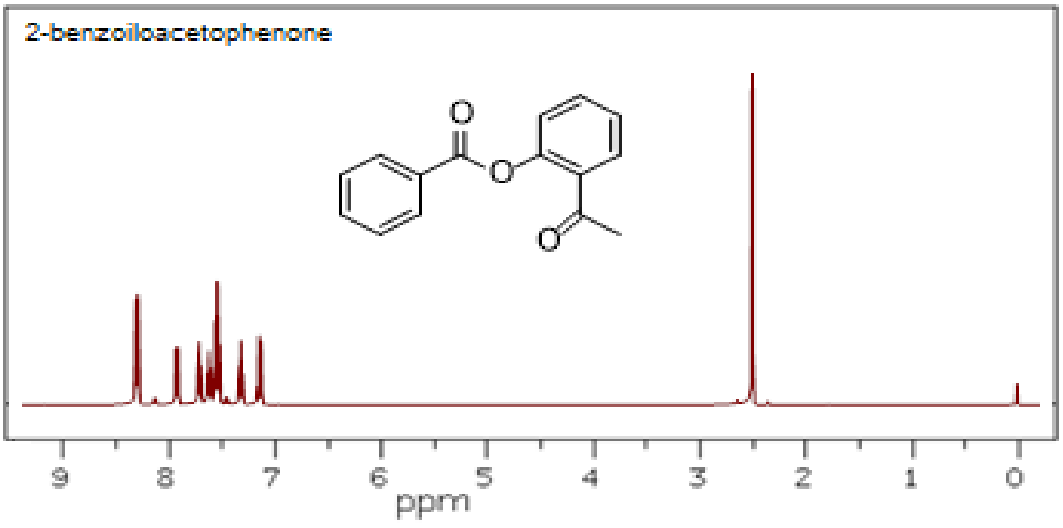
f) ^{13}C NMR spectra of 2-hydroxyacetophenone in $CDCl_3$.



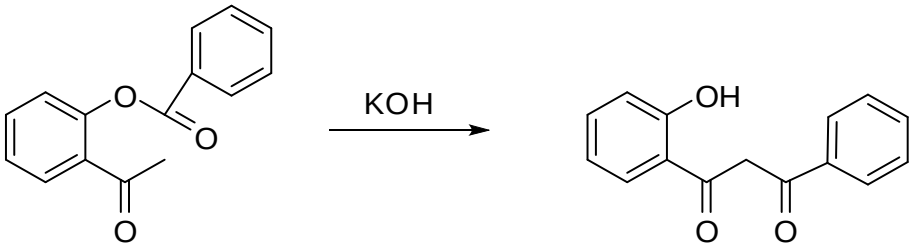
g) FT-IR spectrum of 2-benzoyloxoacetophenone.



h) ^{1}H NMR spectrum of 2-benzoyloxoacetophenone in $CDCl_3$.



STEP 2 2-HYDROXYDIBENZOYLMETHANE



Reagents:		**Instrumentation and glassware:**
2-benzoyloxoacetophenone	4.0 g	round-bottom flask 50 mL
pyridine	15 mL	condenser
granulated KOH	1.4 g	water bath
10% acetic acid	21 mL	magnetic stirrer
methanol		glass rod
		filtering flask with Büchner funnel

All operations should be done under efficiently working fume hood!

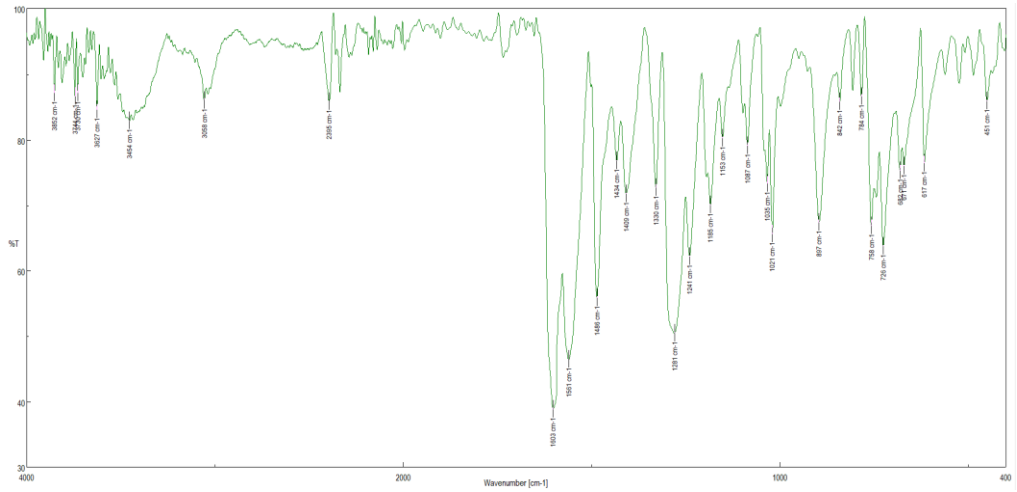
4.0 g of 2-benzoyloxoacetophenone in 15 mL of pyridine in round-bottom flask (50 mL) equipped with condenser place in a water bath and magnetic stirrer, and then heat under reflux to 50 ^{o}C. Next, add 1.4 g of granulated KOH. Mix the reaction mixture for 15 min; if the yellow precipitate of potassium salt prevents stirring, then mix with glass rod. Cool down the reaction mixture to the room temperature and add 21 mL of 10% acetic acid with stirring. Filter yellow precipitate on Büchner funnel, wash with petroleum ether and dry at the 50 ^{o}C. Weight and calculate the yield. Measure the melting point of the 2-hydroxydibenzoylmethane (lit. m.p. 117–120 ^{o}C).
Product obtained is pure enough to be used in the next synthesis step. After recrystallization with methanol, melting point of 2-hydroxydibenzoylmethane is 121–122 ^{o}C.

Thin layer chromatography (TLC):

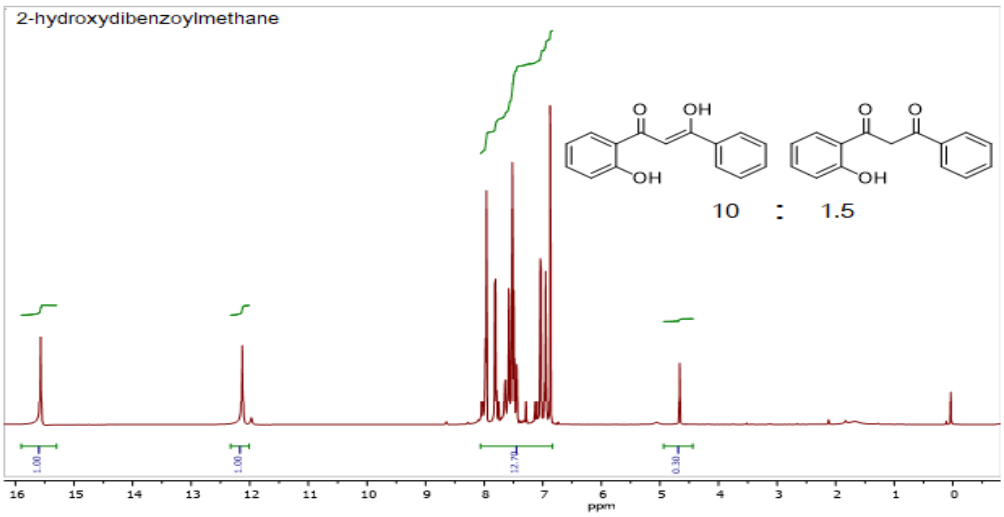
Apply the substrate and product (as a solution in chloroform) onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with *n*-hexane/acetone (7:3). Remove the plate and allow the solvent to evaporate. The spots of the compounds are visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

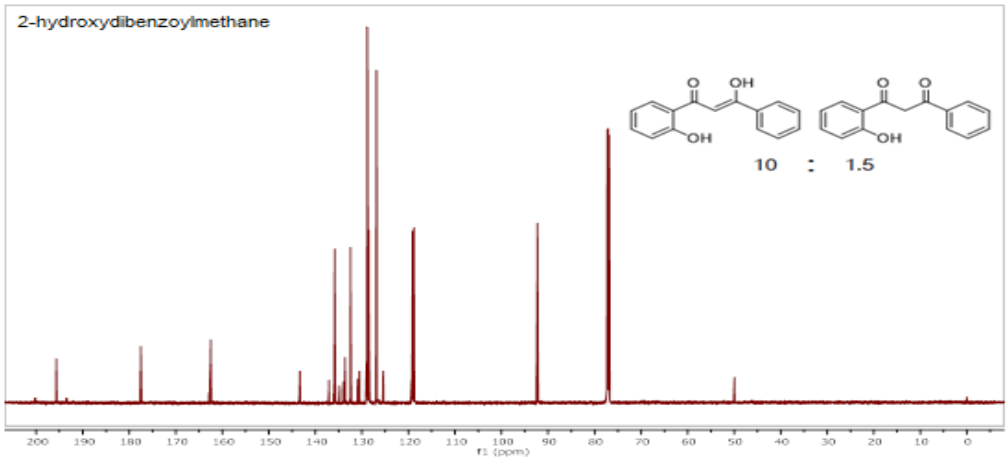
a) FT-IR spectrum of 2-hydroxyacetophenone.



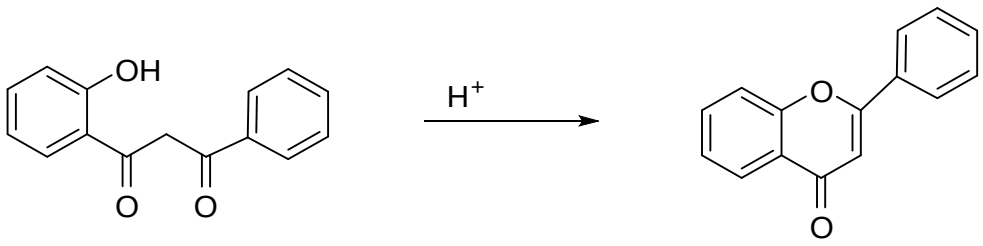
b) ^{1}H NMR spectrum of 2-hydroxyacetophenone in $CDCl_3$ (keto–enol **tautomerism**).



c) ^{13}C NMR spectrum of 2-hydroxyacetophenone in $CDCl_3$ (keto–enol **tautomerism**).



STEP 3 FLAVONE



Reagents:		**Instrumentation and glassware:**
2-hydroxydibenzoylmethane	3.0 g	Round-bottom flask 50 mL
glacial acetic acid	17 mL	beaker 200 mL
conc. H_2SO_4	0.7 mL	condenser
ice and distilled water		water bath
		filtering flask with Büchner funnel

To the solution of 3.0 g 2-hydroxydibenzoylmethane in 17 mL glacial acetic acid placed in round-bottom flask (50 mL) equipped with condenser and water bath, add with stirring 0.7 mL conc. H_2SO_4. Heat the solution for 1 hour, shaking the flask gently from time to time. In the next step, carry the reaction mixture into a beaker (200 mL) with 80 g crushed ice and keep the mixture aside till the ice completely melts. Then, filter the product and wash with water until the filtrate is neutral (approximately 170 mL of water) and dry at the 50 ^oC.

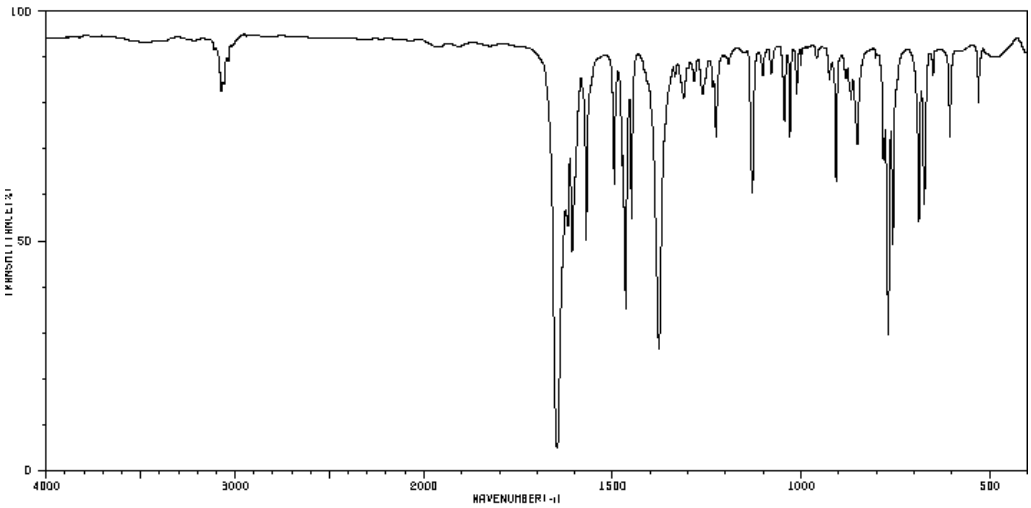
Weigh the product and calculate the yield. Measure the melting point of flavone (lit. m.p. 95–97 ^oC). After recrystallization with large volume of petroleum ether, pure flavone with m.p. 98^oC can be obtained as colorless needles.

Thin layer chromatography (TLC):

Apply the substrate and product (as a solution in chloroform) onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with *n*-hexane/acetone (2:8). Remove the plate and allow the solvent to evaporate. The spots of the compounds are visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

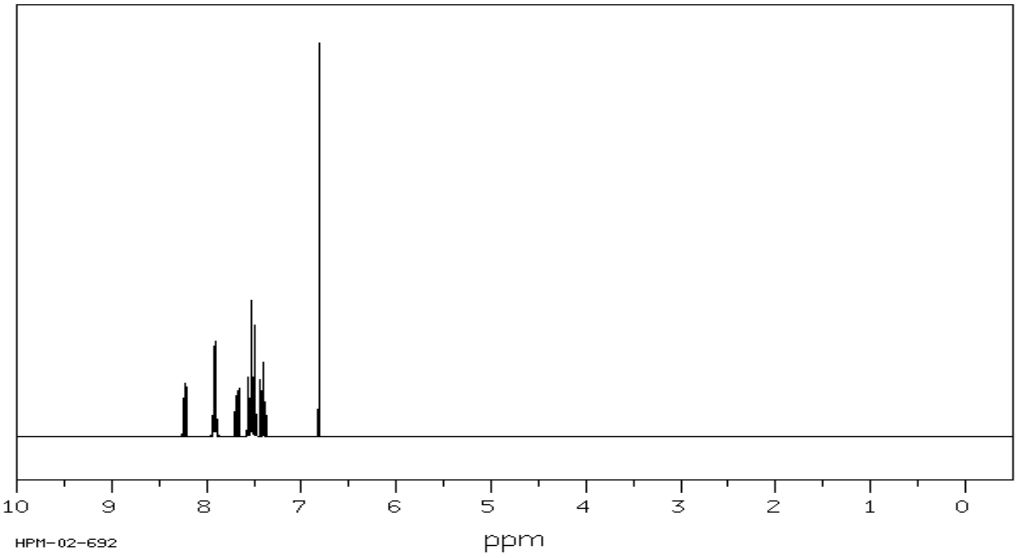
SPECTRA

a) FT-IR spectrum of flavone in KBr disc.

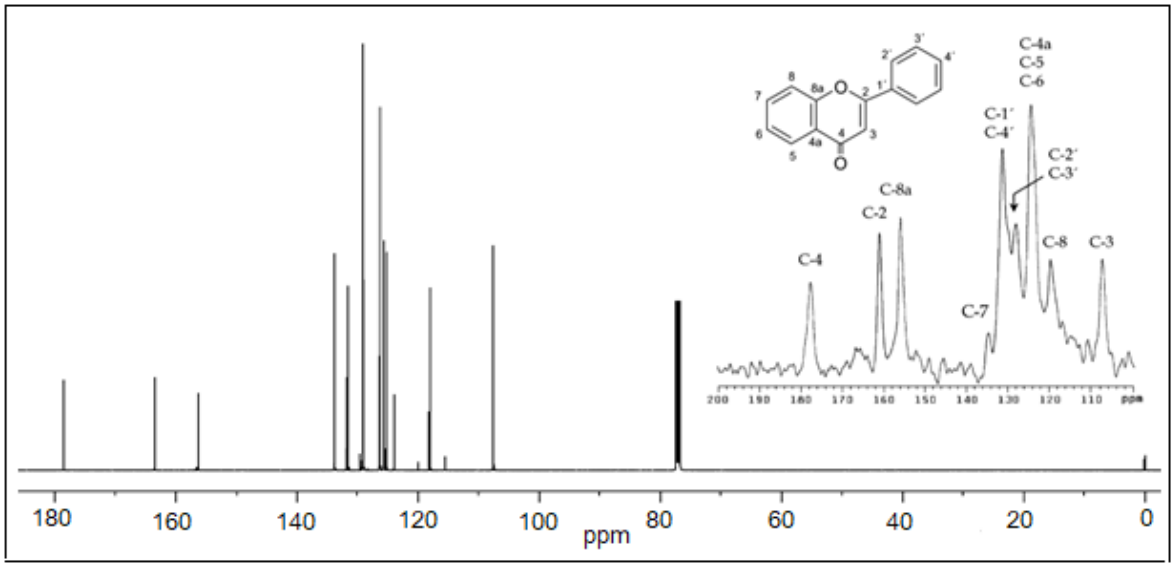


Wavenumber [cm^{-1}]
3072
3058
2869
1646
1618
1607
1570
1496
1449
1311
1044

b) ^{1}H NMR spectrum of flavone in $CDCl_3$.



c) ^{13}C NMR spectrum of flavone in $CDCl_3$.



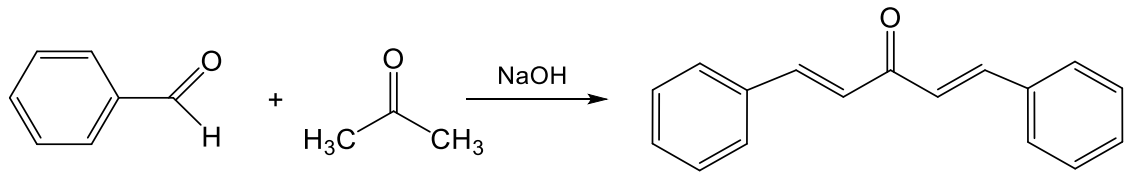
References

https://www.chemicalbook.com

Bansal M., Kaur K., Tomar J., Kaur L.: Synthesis of Flavones. *Biomed J Sci & Tech Res.*, 1 (6) (2017) 1752-1755.

Kshatriya R. B., Shaikh Y. I., Nazeruddin G. M.: Synthesis of Flavone Skeleton by Different Methods. *Orient. J. Chem.*, 29(4) (2013) 1475-1487.

16. DIBENZYLIDENEACETONE



Reagents:

benzaldehyde	0,02 mol (d=1,0415 g/mL)
acetone	0,01 mol (d=0.791g/mL)
NaOH	2 g
ethanol	27 mL
ethyl acetate	5 mL

Instrumentation and glassware:

three-necked round-bottomed flask 250 mL
dropping funnel (10 mL)
thermometer
filtering flask with Büchner funnel
water bath
stirrer
beaker 100 mL
Petri dish

In a three-necked round-bottomed flask (250 mL) with magnetic stirrer, thermometer and dropping funnel place the cold solution **A**: of NaOH in 34 mL of water and 27 mL of ethanol. Prepare in the dropping funnel mixture **B:** mix together benzaldehyde 0,02 mol (d=1,0415 g/mL) and acetone 0,01 mol (d=0.791g/mL - calculate the amount of the reagents!).

Cool down to room temperature the mixture **A** (keep water bath temp. 20-25 ^{o}C) and drop half of the mixture **B**. Stir vigorously and after 15 minutes add additional portion of this mixture **B**. Stir additionally 30 minutes. Then shake the flask with reaction mixture.

Filter the yellow solid on Büchner funnel, wash with water up to pH=7 (check pH for base with pH paper) and dry on air on Petri dish. Recrystallize the crude product from ethyl acetate or ethanol (5 mL). Filter the crystals on Büchner funnel and dry on air. Weight the product, calculate the percentage yield and measure the m.p. (lit. 112-113 ^{o}C).

Thin layer chromatography (TLC):

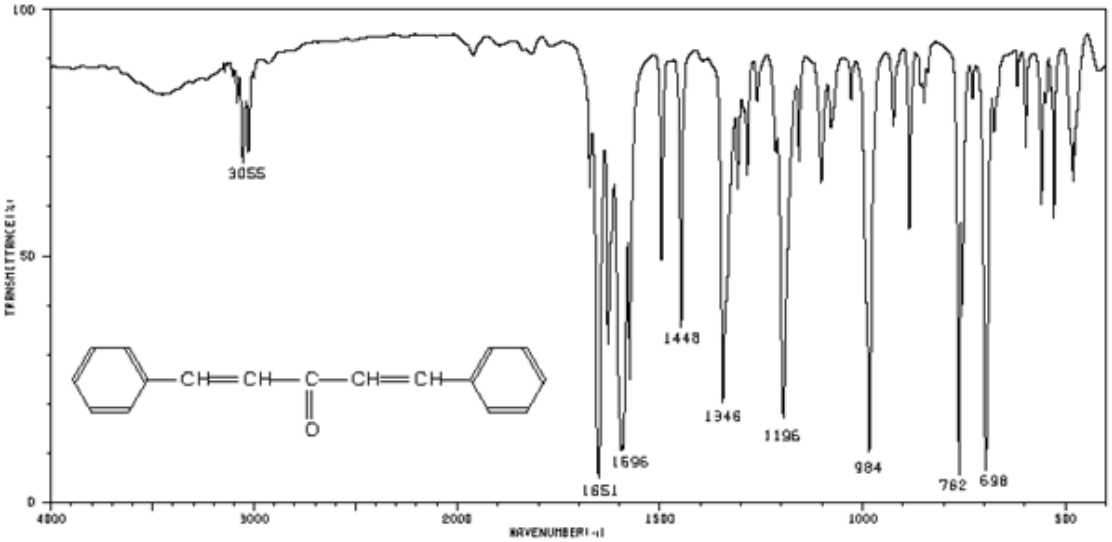
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate into developing tank (small beaker, covered with glass plate). Develop with $CHCl_3$/EtOH (9:1).

The spot of product is visible in the UV light. Mark the spots in pencil. Then, using forceps, dip the plate into the mixture of SiO_2/I_2

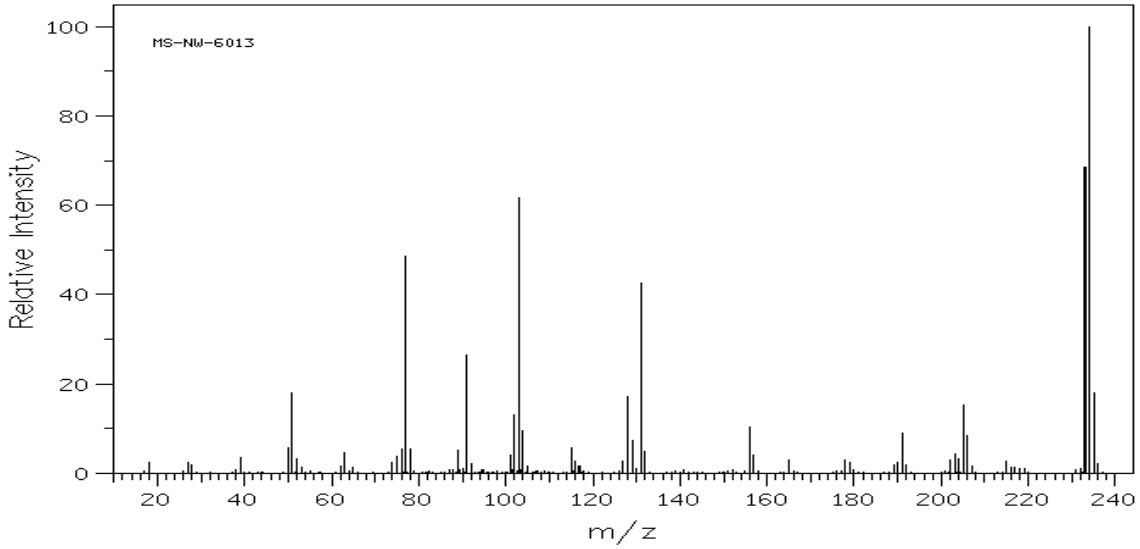
SPECRTA

MS, FT-IR and **NMR** spectra of benzaldehyde find in chapter 14. Chalcone.

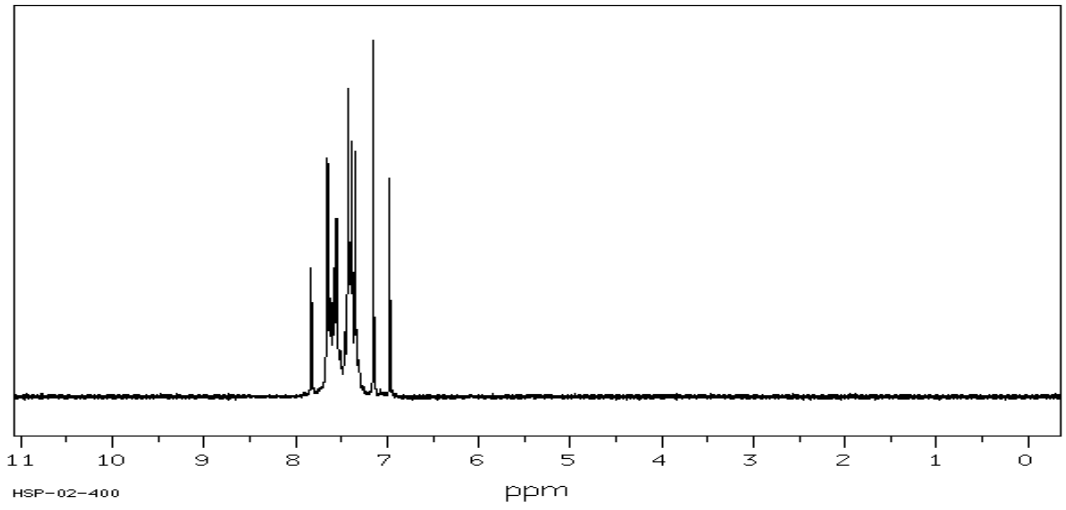
a) FT IR spectrum of dibenzylideneacetone (KBr).



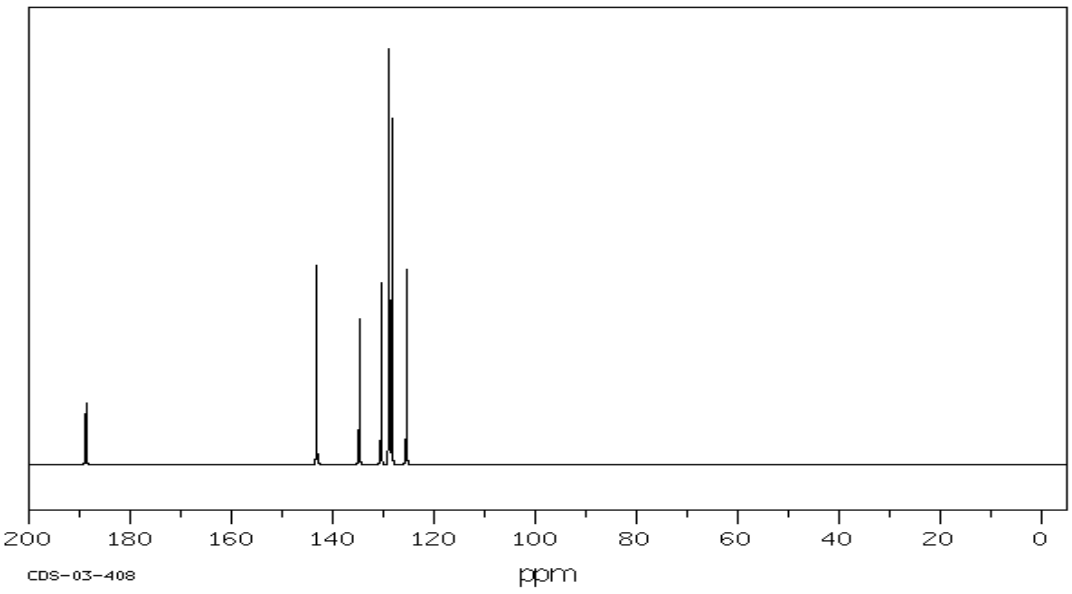
b) EI-MS spectrum of Dibenzylideneacetone.



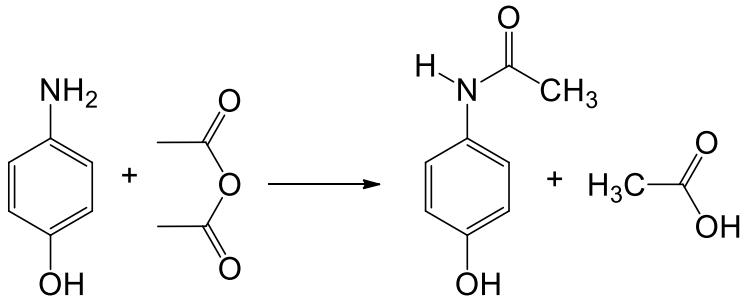
c) ^{1}H NMR spectrum of dibenzylideneacetone in $CDCl_3$.



d) ^{13}C NMR spectrum of dibenzylideneacetone in $CDCl_3$.



17. PARACETAMOL (4-ACETAMINOPHENOL)



Reagents:

p-aminophenol	5.5 g
acetic anhydride	6 mL
model compound - a pill of APAP®	
or Paracetamol®	

Instrumentation and glassware:

heating mantle
round-bottom flask 50 mL
condenser
filtering flask with Büchner funnel
beaker 100 mL
glass rod
Petri dish

To a round-bottom flask (100 mL) place 5.5 g of *p*-aminophenol, and 15 mL of distilled water. Add carefully by slow dropping 6 mL of acetic anhydride. Adjust the Liebig condenser and heat the mixture under reflux for 20 minutes. After the substrate has dissolved, cool down the solution, the crystals should appear in the flask. Filter the product using a Büchner funnel and wash it with cold water to pH = 7 of the filtrates.

Recrystallize the obtained crude product from 20 mL of water (heat under reflux). Next pour the hot solution into small beaker and cool down in an ice-water bath. Filter the product on a Büchner funnel, and dry on a Petri dish.

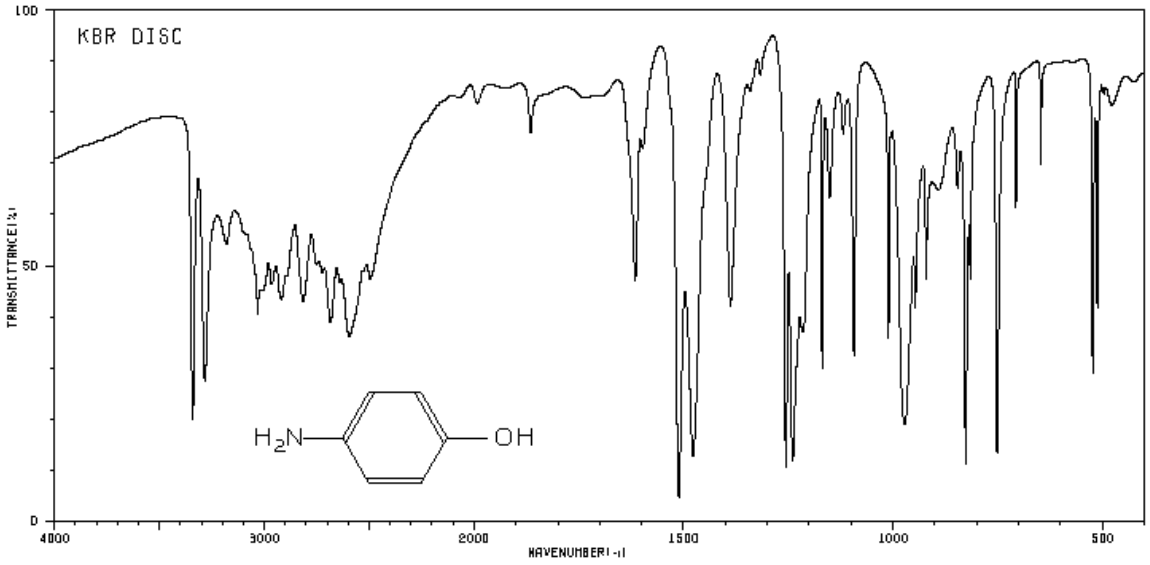
Weigh the product, calculate the yield and measure the m.p. (lit. m.p. 169 ^{o}C).

Thin layer chromatography (TLC):

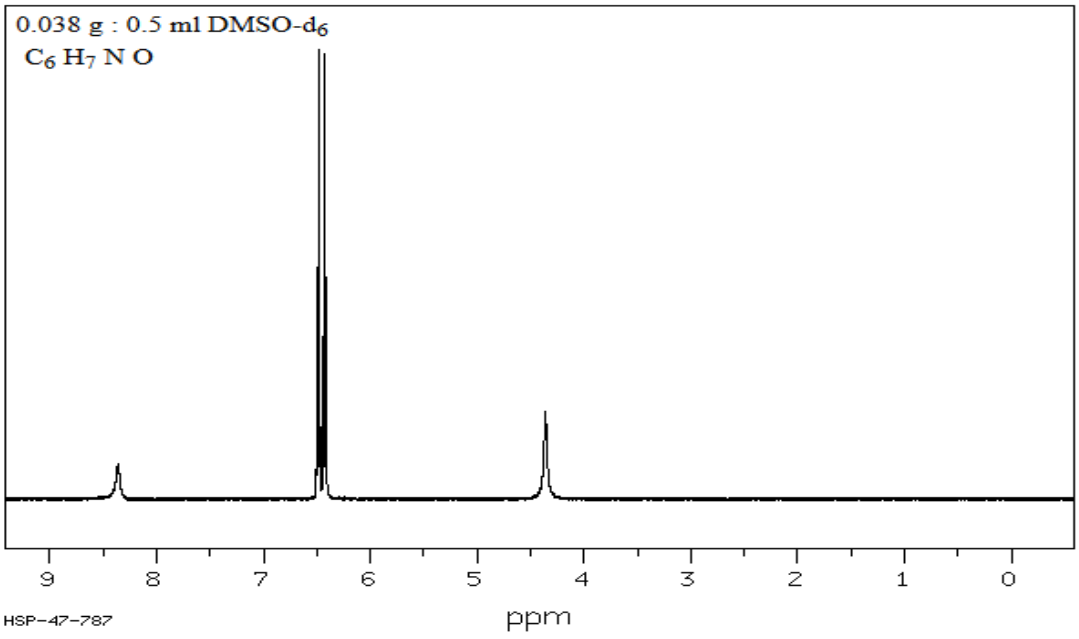
Apply the substrate and product (as a solution in MeOH) onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with chloroform/methanol (9:1). Remove the plate and allow the solvent to evaporate. The spot of paracetamol is visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

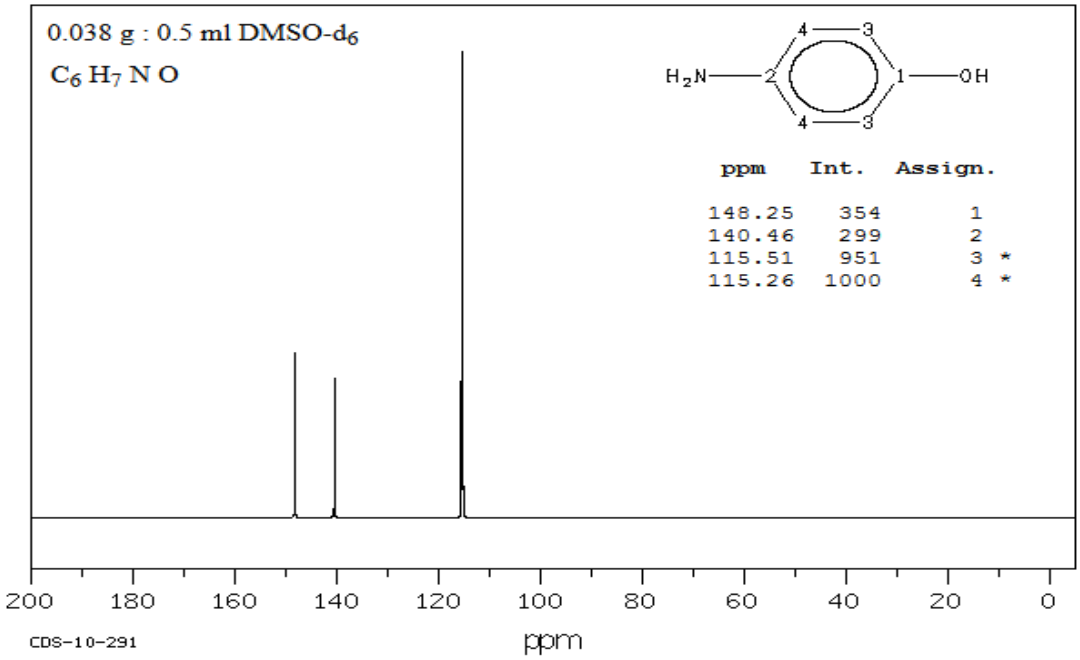
a) FT-IR spectrum of *p*-aminophenol in KBr disc.



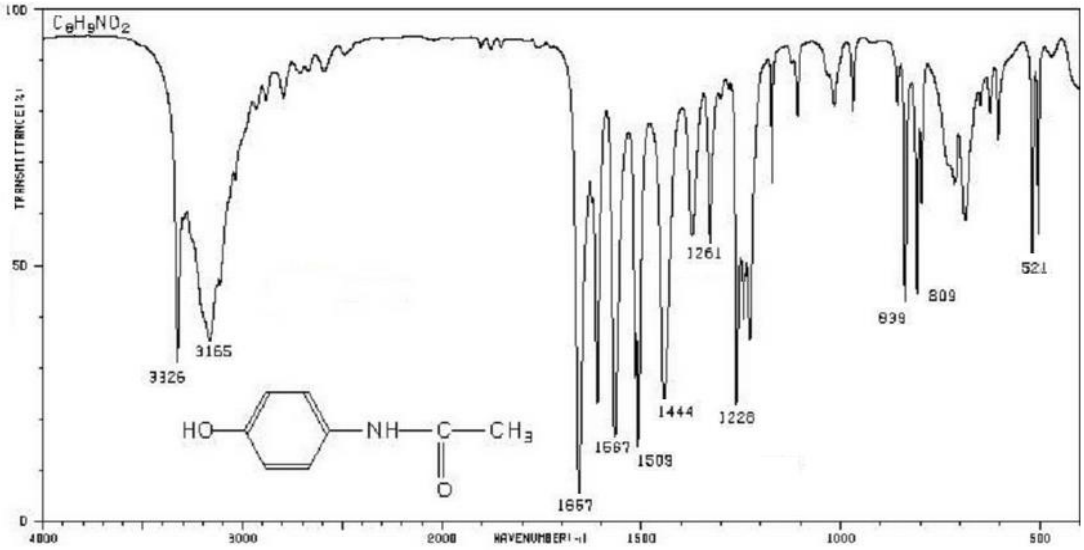
b) ^{1}H NMR spectrum of *p*-aminophenol in DMSO-d_6.



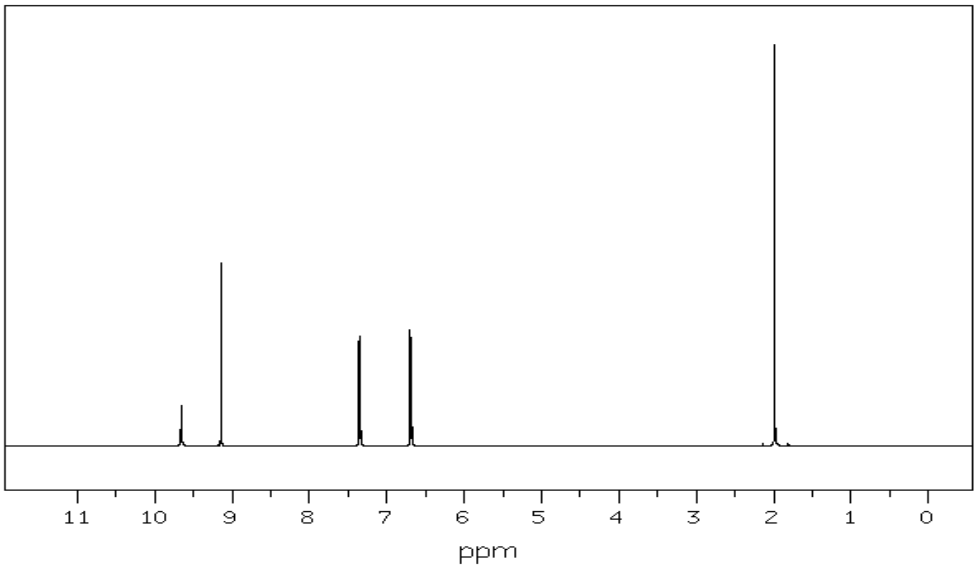
c) ^{13}C NMR spectrum of *p*-aminophenol in DMSO-d_6.



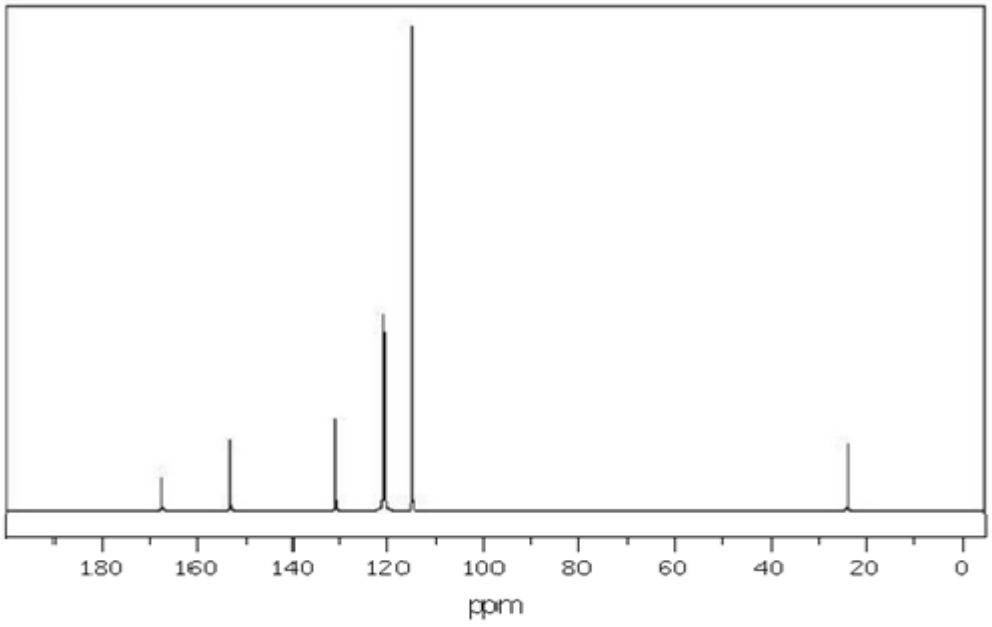
d) FT-IR spectrum of paracetamol in KBr disc.



e) ^{1}H NMR spectrum of paracetamol in DMSO-d_6.

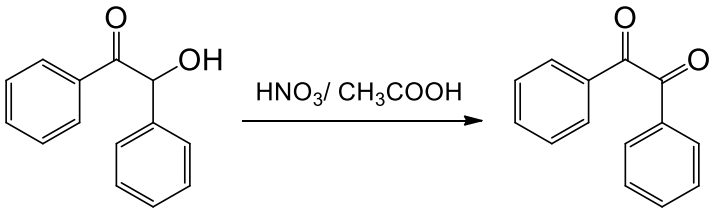


a) ^{13}C NMR spectrum of paracetamol in DMSO-d_6.



18. PHENYTOIN (2-step synthesis)

STEP 1 BENZIL



Reagents:		**Instrumentation and glassware:**
benzoin	4.0 g	round-bottom flask 100 mL
anh. acetic acid	20 mL	crystallizing dish
conc. HNO_3	10 mL	heating mantle
ethanol	10 mL	stirrer
pH paper		gas supply pipe
CH_2Cl_2		beaker 200 mL
		filtering flask with Büchner funnel
		Petri dish

Work under hood!

Place 4.0 g of benzoin and 20 mL of acetic acid in 100 mL round-bottom flask. Condenser has to be equipped with the appropriate glassware to remove toxic vapors of nitrogen oxides. While working under a fume hood, add 10 ml conc. HNO_3 and heat the mixture under reflux for 1 hour or more until the yellow vapors disappear. Check the reaction progress with TLC (use CH_2Cl_2 as mobile phase).

After the substrate reacted completely, cool the mixture and pour it into the 200 mL beaker with 40 g of ice and 20 mL of water. Stir until the separated oil solidifies. Filter the crude dibenzoyl on Büchner funnel and wash thoroughly with water (check the filtrate for acid with pH paper). Product can be recrystallized from ethanol (10 mL).

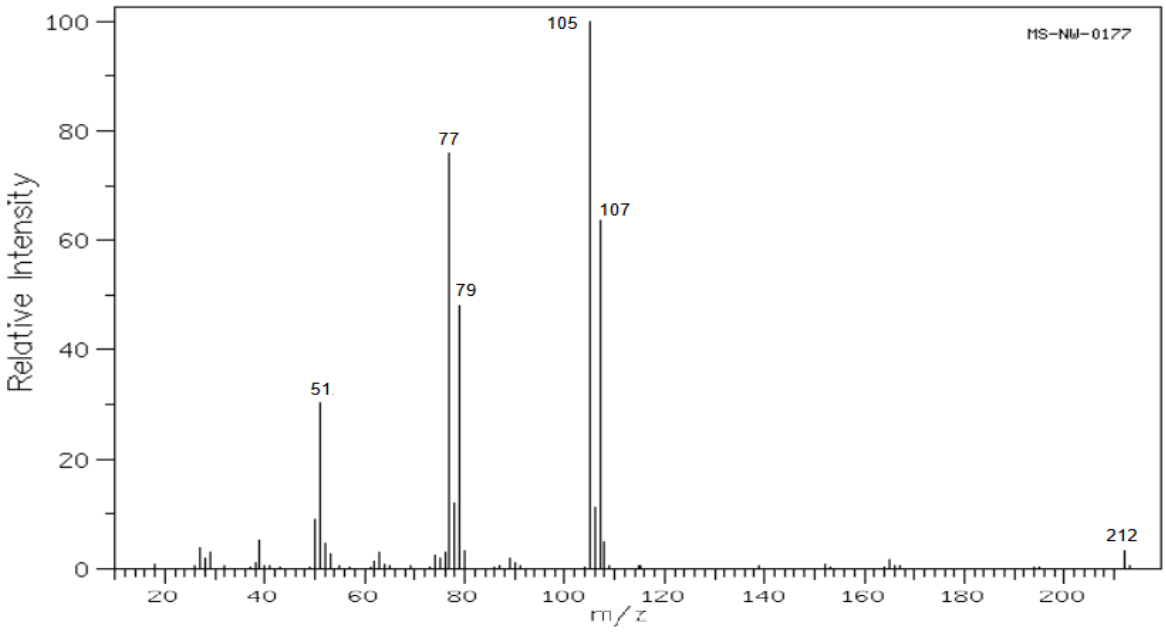
Weight the product, calculate the yield and measure the m.p. (lit. m.p. 94–96 ^oC).

Thin layer chromatography (TLC):

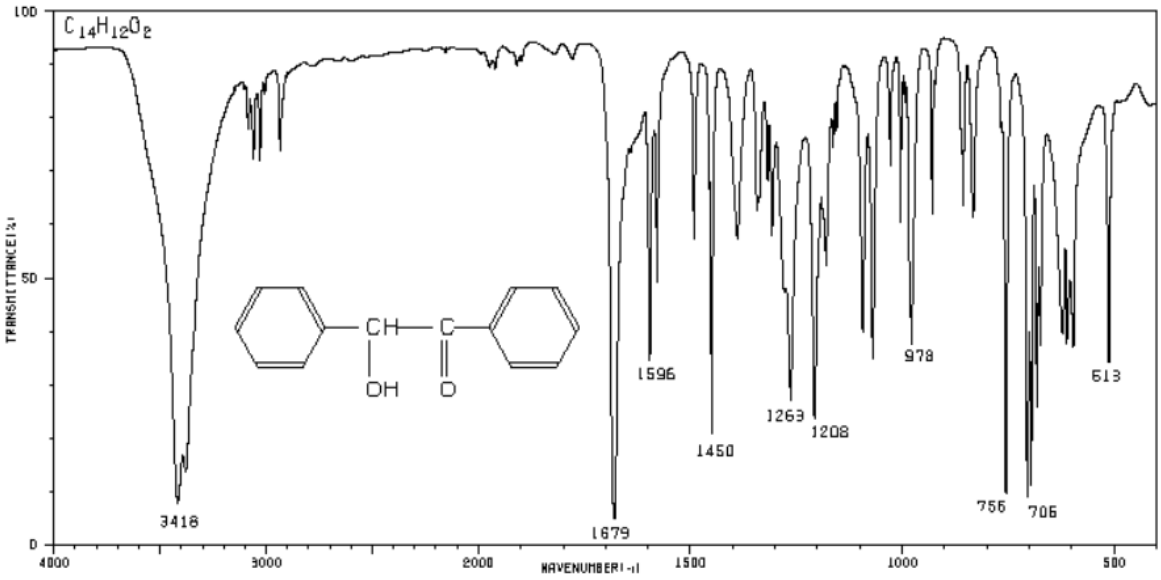
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with CH_2Cl_2 or *n*-hexane/ethyl acetate (8:2). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

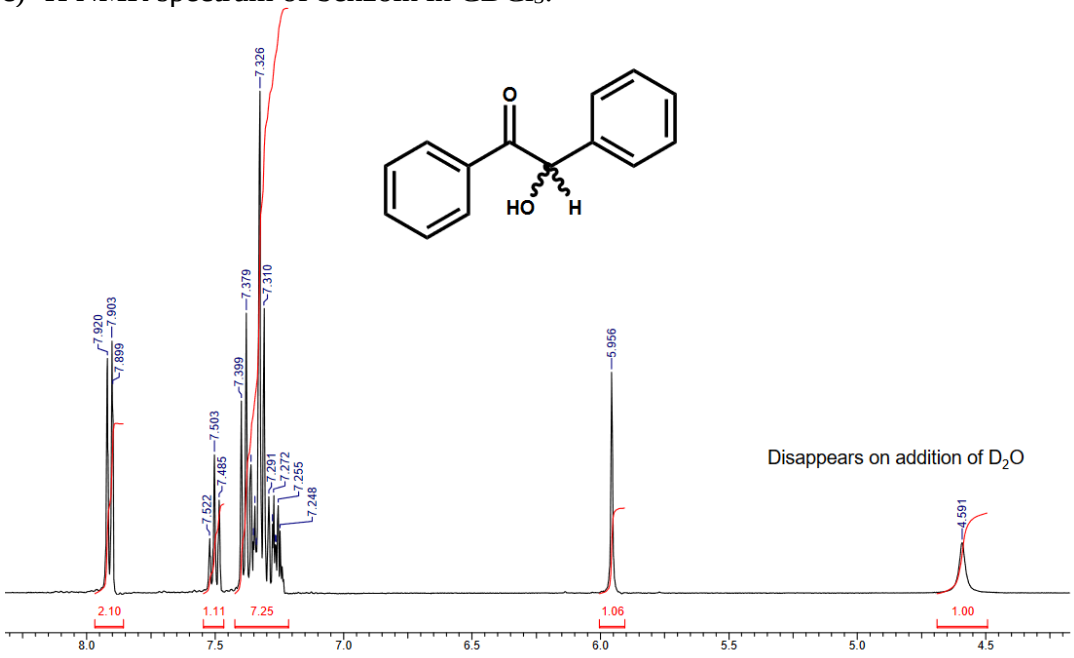
a) EI-MS spectra of benzoin.



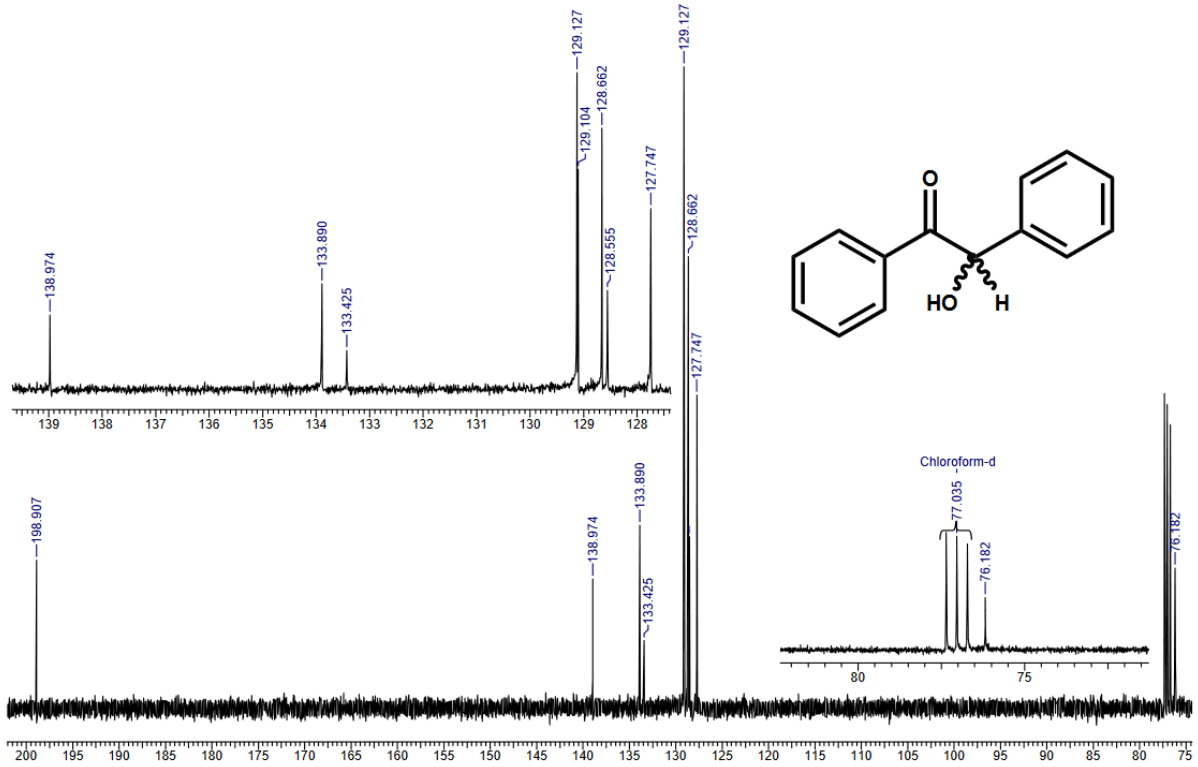
b) FT-IR spectrum of benzoin in KBr disc.



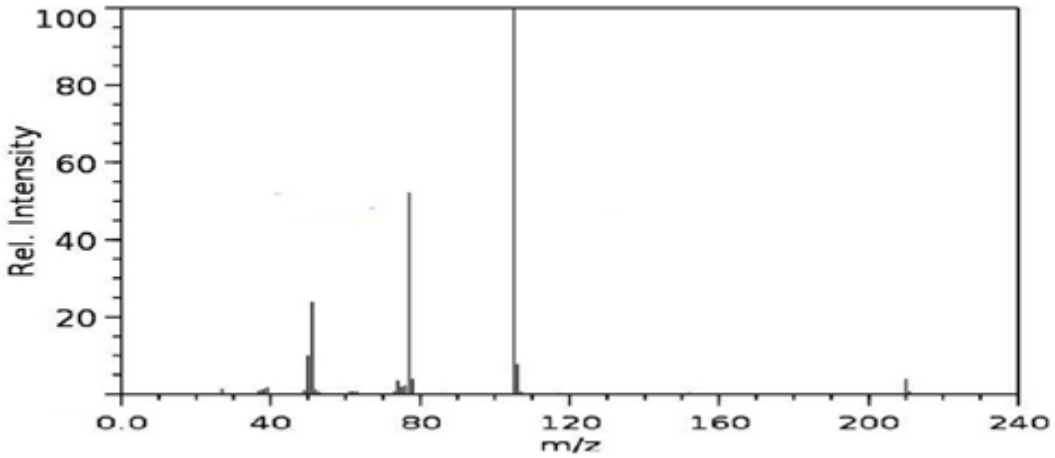
c) ^{1}H NMR spectrum of benzoin in $CDCl_3$.



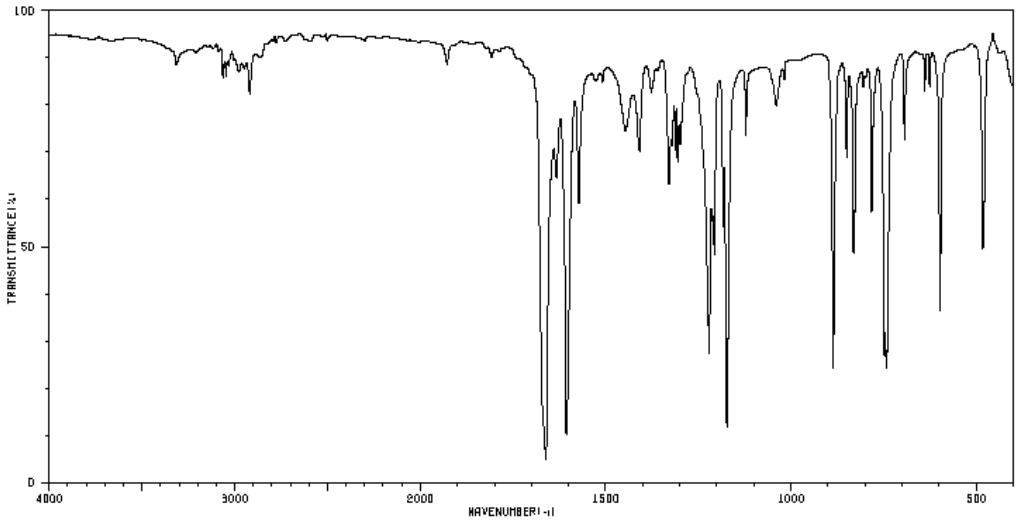
d) ^{13}C NMR spectrum of benzoin in $CDCl_3$.



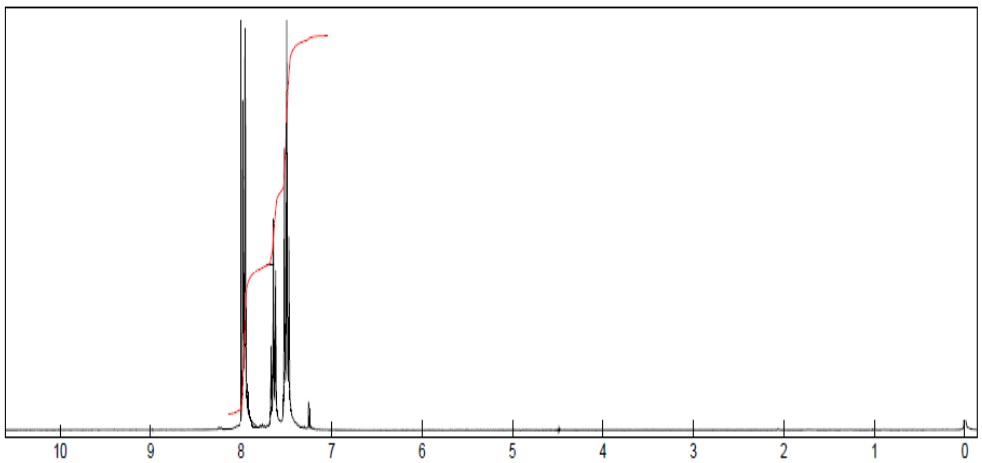
e) EI-MS spectra of benzil.



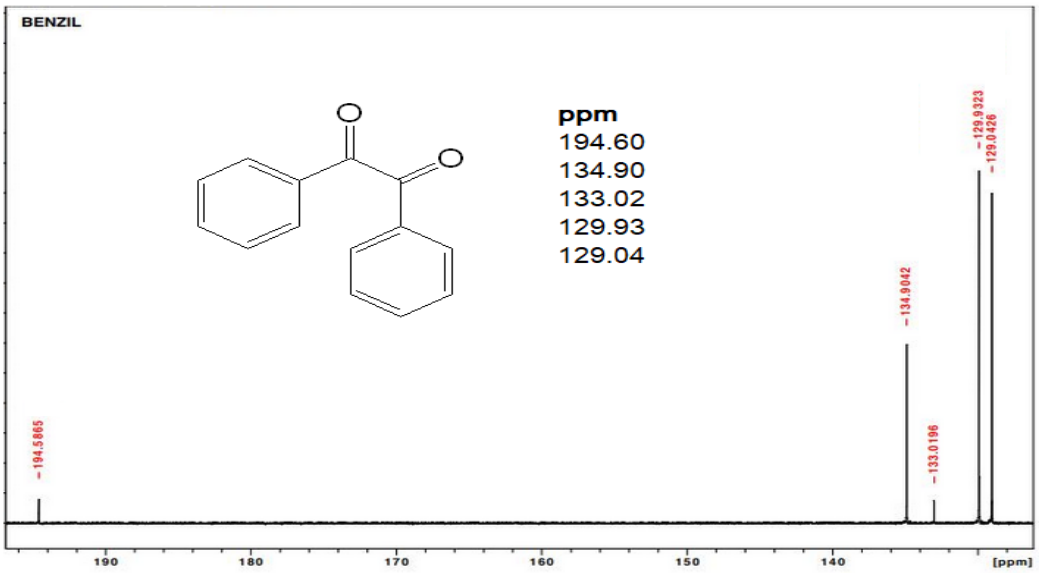
f) FT-IR spectrum of benzil in KBr disc.



g) ^{1}H NMR spectrum of benzil in $CDCl_3$.



h) ^{13}C NMR spectrum of benzil in $CDCl_3$.

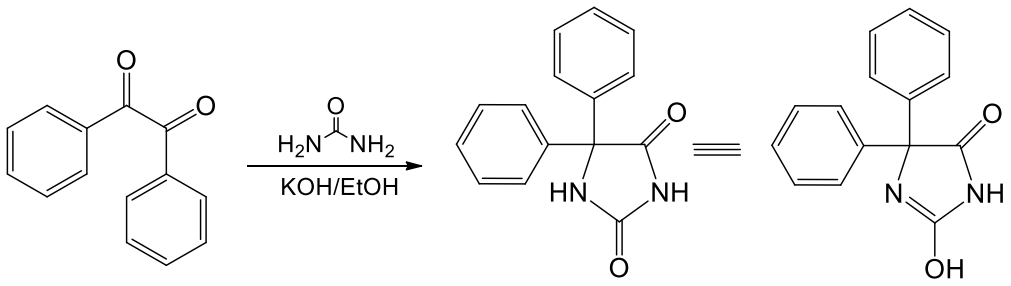


References

https://www.chegg.com/homework-help/questions-and-answers/interpret-1-h-13c-nmr-spectra-benzil--label-different-types-protons-carbons-com.p.ound-locat-q27496581

https://instruct.uwo.ca/chemistry/283g/labs/Experiment%202/Spectral%20Data%20Exp%202%20_2007.pdf

STEP 2 PHENYTOIN



Reagents:

benzil	2.00 g
urea	0.96 g
95% ethanol	66 mL
9 M KOH	6 mL
CH_2Cl_2	10 mL
10% HCl	

Instrumentation and glassware:

round-bottom flask 100 mL
reflux condenser
crystallizing dish 500 mL
heating mantle
stirrer
beaker 400 mL
filtering flask with Büchner funnel
graduated cylinders 100 mL and 50 mL
Petri dish

Use rubber gloves when working with chemicals!

Place 2.0 g of dibenzoyl in 100 mL round-bottom flask, add 0.96 g urea and 50 mL of ethanol. Stir until reagents dissolve. Add 6 mL of 9 M KOH and reflux for 2 hours. Check the reaction progress with TLC (CH_2Cl_2 as mobile phase).

After the reaction is completed, filter off the precipitate and pour the filtrate into 400 mL beaker and add ice-water mixture (50 g + 50 mL). Put the beaker into ice bath made from the crystallizing dish, and add dropwise 10% HCl until the pH of the mixture reaches 4–5.

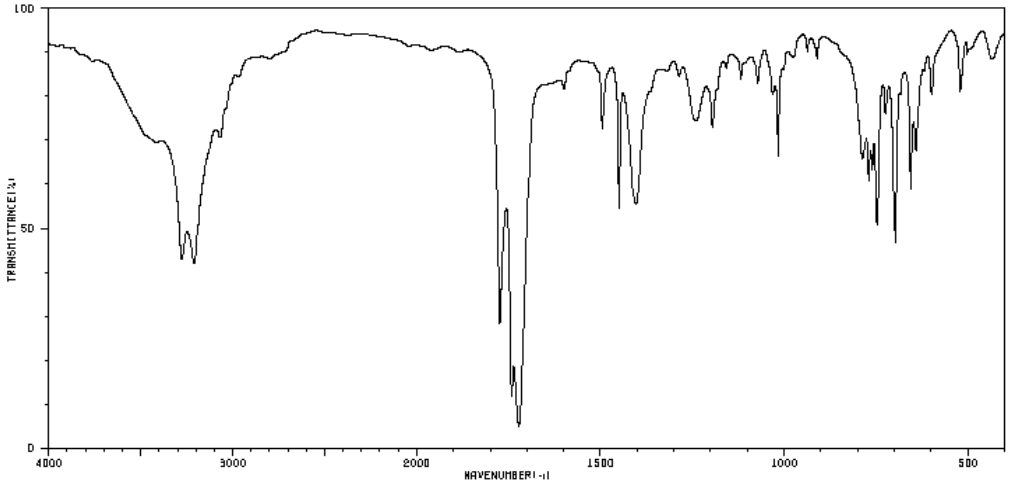
Filter the ice-cold mixture. Recrystallize crude product from the ethanol-water mixture (8:2). Weigh the product, calculate the yield and check the melting point (lit. m.p. 293–294 ^oC).

Thin layer chromatography (TLC):

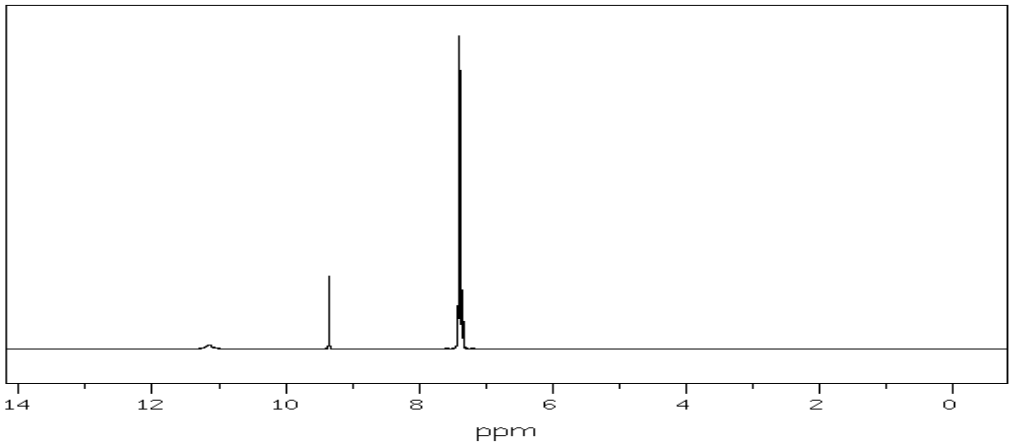
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with CH_2Cl_2 or *n*-hexane/ethyl acetate (8:2). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

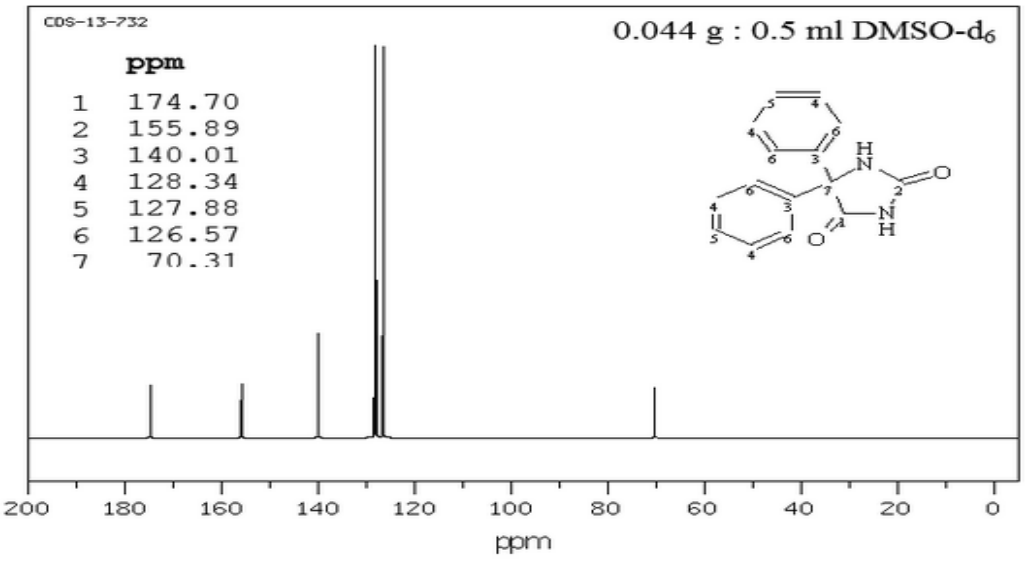
a) FT-IR spectrum of phenytoin in KBr disc.



b) ^{1}H NMR spectrum of phenytoin in DMSO-d_6.

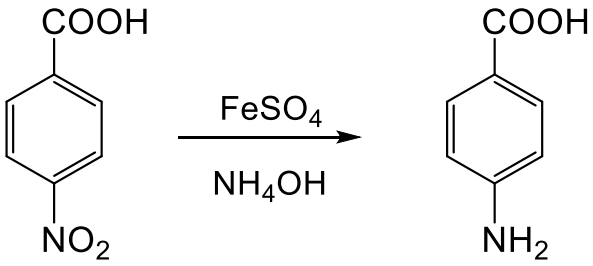


c) ^{13}C NMR spectrum of phenytoin in DMSO-d_6.



19. BENZOCAINE (2step synthesis)

STEP 1 4–AMINOBENZOIC ACID



Reagents:		**Instrumentation and glassware:**
4-nitrobenzoic acid	2.1 g	Erlenmeyer flask 250 mL
12% NH_4OH	15 mL	round-bottom flask 250 mL
25% NH_4OH	20 mL	filtering flask with Büchner funnel
$FeSO_4x7H_2O$	44 g	round-bottom flask 50 mL
citric acid		graduated cylinders 100 mL
ethyl acetate		beaker 250 mL
CH_2Cl_2		stirrer
Celite		crystallizing dish 500 mL

In a round-bottom flask (250 mL) with magnetic stirrer place 44 g of $FeSO_4x7H_2O$ in 50 mL H_2O and boil it. In the meantime, dissolve in Erlenmeyer flask (250 mL) 2.1 g of 4-nitrobenzoic acid in 15 mL 12% NH_4OH (place the flask in the water bath and heat slightly to dissolve the solid compound). Add dropwise this solution to the flask with $FeSO_4$ salt and stir vigorously till the forming product prevents stirring. Then, shake the flask with reaction mixture. After 20 minutes, add slowly 15 mL of 25% NH_4OH up to pH = 9 (check pH for base with pH paper). Stir additionally 20 minutes. Then, filter the hot brown mixture on Büchner funnel with Celite cake. **Take care of "mother liquor"! There is your product.**

Note! The product dissolve easily in water, ethanol and diethyl ether!

Important is the solution!!!! Acidify it with citric acid to pH = 4 and move the mixture to separatory funnel and extract (5 x 30 mL) with the mixture ethyl acetate/CH_2Cl_2 1:2 (v/v). Combine the organic layers and dry the extract over $MgSO_4$, then filtrate through the funnel with cotton plug to remove $MgSO_4$. Transfer the combined fractions into a clean, dry and weighted round-bottom flask (100 mL) and concentrate the solution on rotary evaporator.

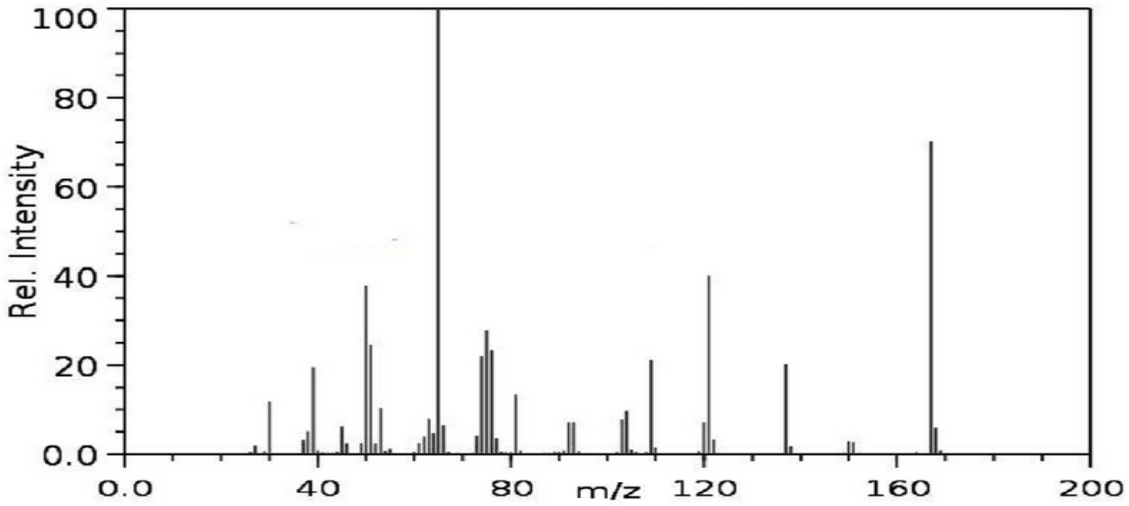
The crude yellow crystals of 4-aminobenzoic acid will be used to the second step of reaction. Measure the m.p. (lit. m.p. 192 ^oC).

Thin layer chromatography (TLC):

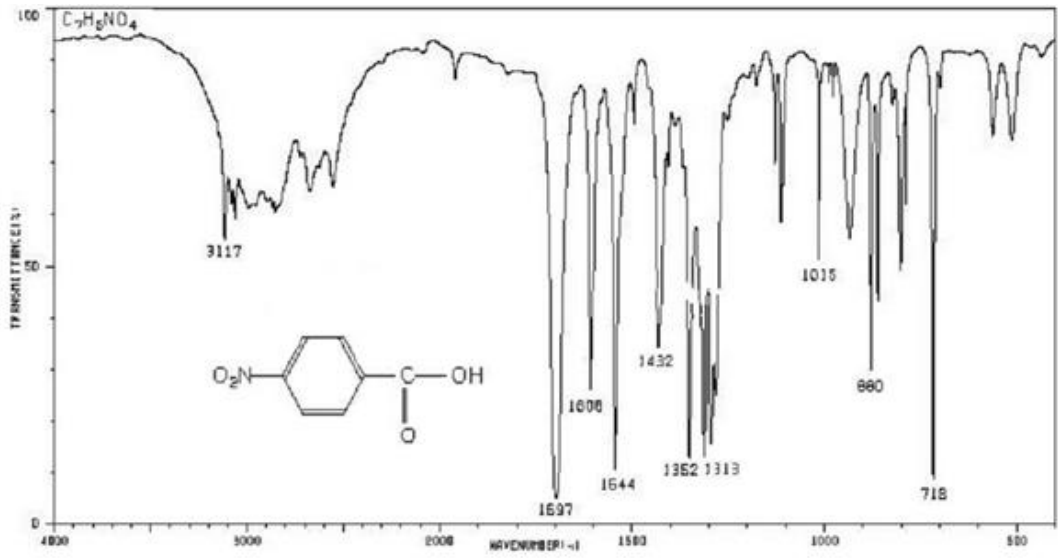
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with CH_2Cl_2/MeOH (8:2). Mark the spots with pencil under UV light.

SPECTRA

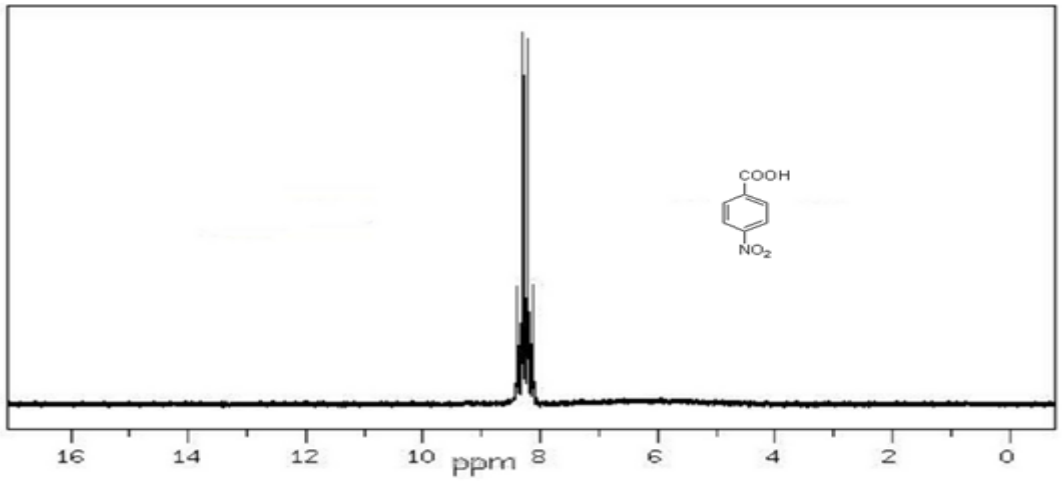
a) EI-MS spectrum of 4-nitrobenzoic acid.



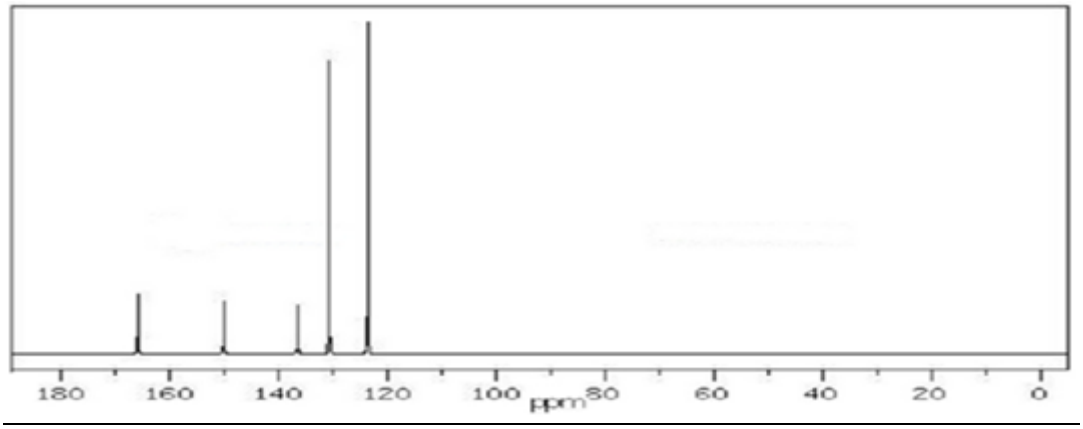
b) FT-IR spectrum of 4-nitrobenzoic acid in KBr disc.



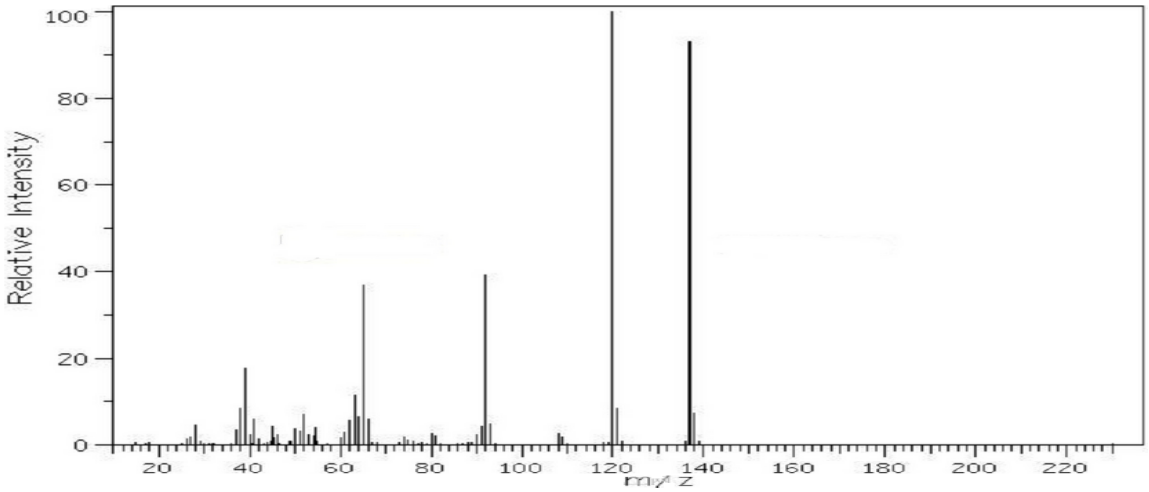
c) ^{1}H NMR spectrum of 4-nitrobenzoic acid in DMSO-d_6.



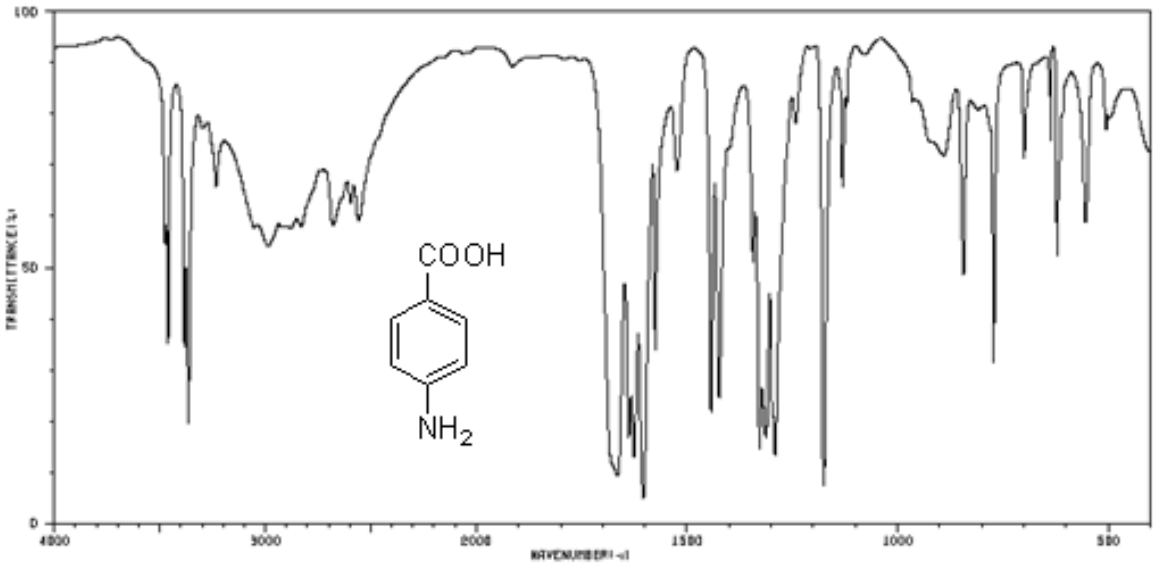
d) ^{13}C NMR spectrum of 4-nitrobenzoic acid in DMSO-d_6.



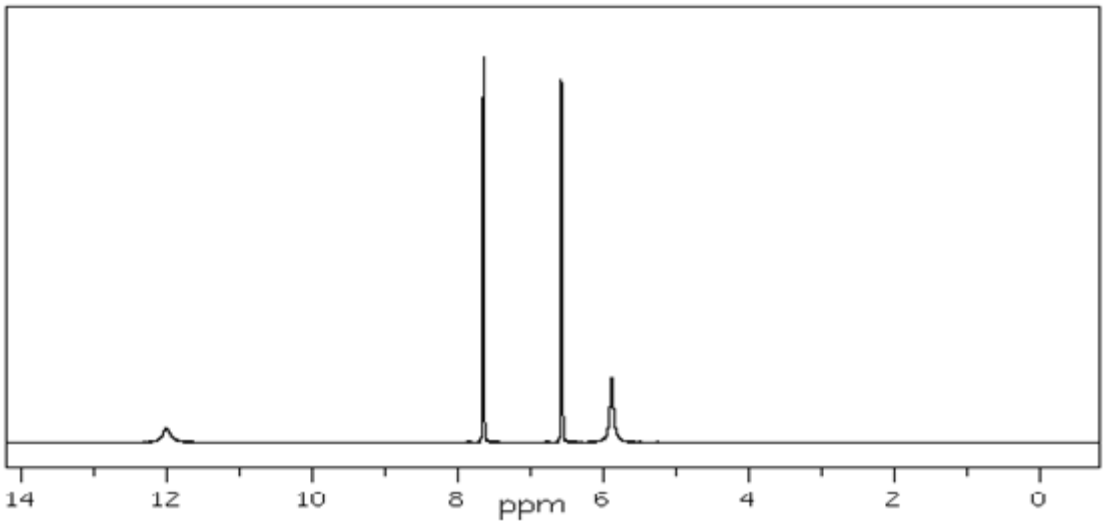
e) EI-MS spectrum of 4-aminobenzoic acid.



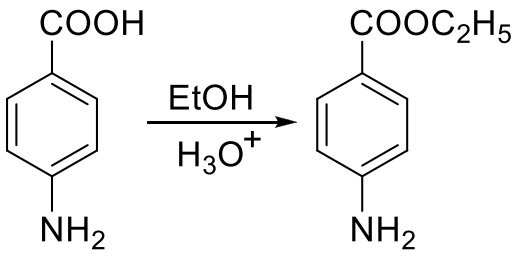
f) FT-IR spectrum of 4-aminobenzoic acid in KBr disc.



g) ^{1}H NMR spectrum of 4-aminobenzoic acid in DMSO-d_6.



STEP 2 ETHYL 4-AMINOBENZOATE (BENZOCAINE)



Reagents:

4-aminobenzoic acid	1.0 g
abs. EtOH	8 mL
H_2SO_4 (10% oleum)	0.6 mL
5% NH_4OH	~5 mL
pH papers	

Instrumentation and glassware:

round-bottom flask 100 mL or 50 mL
condenser
separatory funnel
Erlenmeyer flask 100 mL
filtering flask with Büchner funnel
graduated cylinder 100 mL
beaker 100 mL
heating mantel
Petri dish

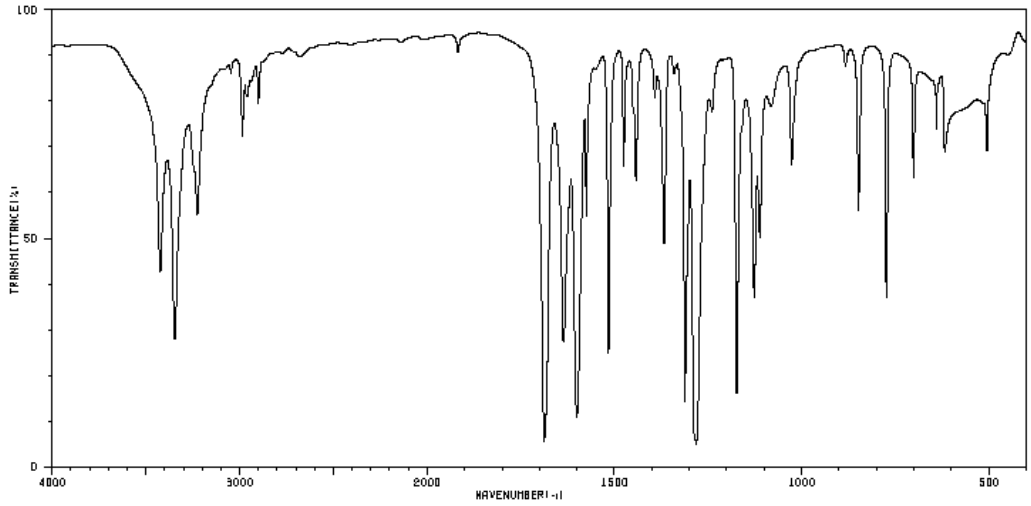
In a round-bottom flask (100 mL), place 1.0 g of 4-aminobenzoic acid, 8 mL anh. ethanol and 0.6 mL of 10% oleum. Adjust the Liebig condenser and heat under reflux for 4 hours. Cool down the mixture and alkalize with aq. NH_4OH to pH=10. Move the mixture to separatory funnel and extract with ethyl acetate (3 x 30 mL). Combine the organic layers and wash these fractions with NaCl solution. Dry the extract over $MgSO_4$, then filtrate through the funnel with cotton plug to remove $MgSO_4$. Transfer the combined fractions into a clean and dry round-bottom flask (100 mL) and concentrate the solution on rotary evaporator. Recrystallize the crude product from chloroform. Filter the crystals on Büchner funnel, and dry on air on Petri dish. Weight the product, calculate the percentage yield and measure the m.p. (lit. m.p. 92 ^oC).

Thin layer chromatography (TLC):

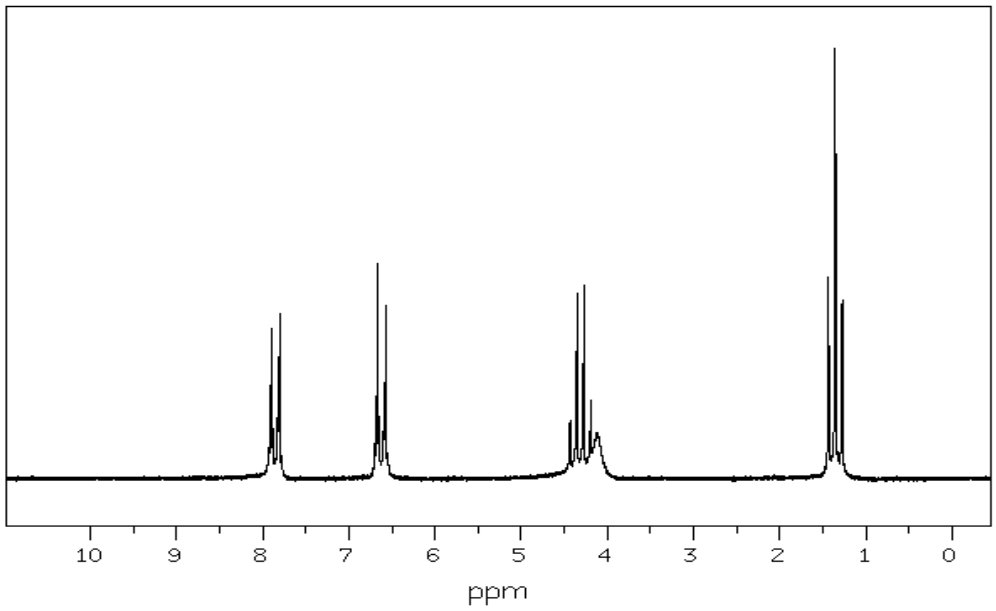
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with CH_2Cl_2/MeOH (8:2). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

a) FT-IR spectrum of benzocaine in KBr disc.

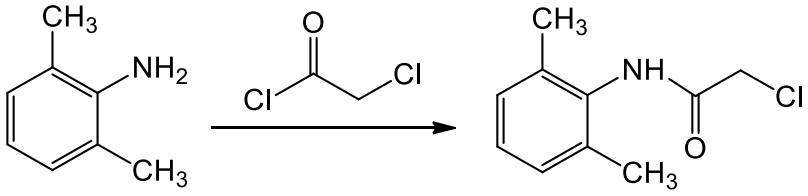


b) ^{1}H NMR spectrum of benzocaine in $CDCl_3$.



20. LIDOCAINE (2-step synthesis)

STEP 1 2–CHLORO-2,6-DIMETHYLACETANILIDE



Reagents:		**Instrumentation and glassware:**
2,6-dimethylaniline	0.5 g	crystallizing dish 500 mL
anh. CH_3COOH	3.6 mL	stirrer with heating
chloroacetyl chloride	0.37 mL	Erlenmeyer flask 50 mL
sodium acetate	0.75 g	Erlenmeyer flask 25 mL
toluene	4.5 mL	filtering flask with Büchner funnel
diethylamine	0.42 mL	graduated cylinder 25 mL
pH papers		Petri dish

Carry out the following reaction in the fume hood!

In a clean, dry 50 mL Erlenmeyer flask, mix 0.5 g of 2,6-dimethylaniline, 3.6 mL of glacial acetic acid, and 0.37 mL of chloroacetyl chloride (in that order), under the fume hood.

Carefully warm this mixture in a hot water bath with swirling for 4 minutes (use hot tap water), remove from the bath, and add a solution of 0.75 g of sodium acetate in 15 mL of distilled water (previously prepared in a 25 mL Erlenmeyer flask).

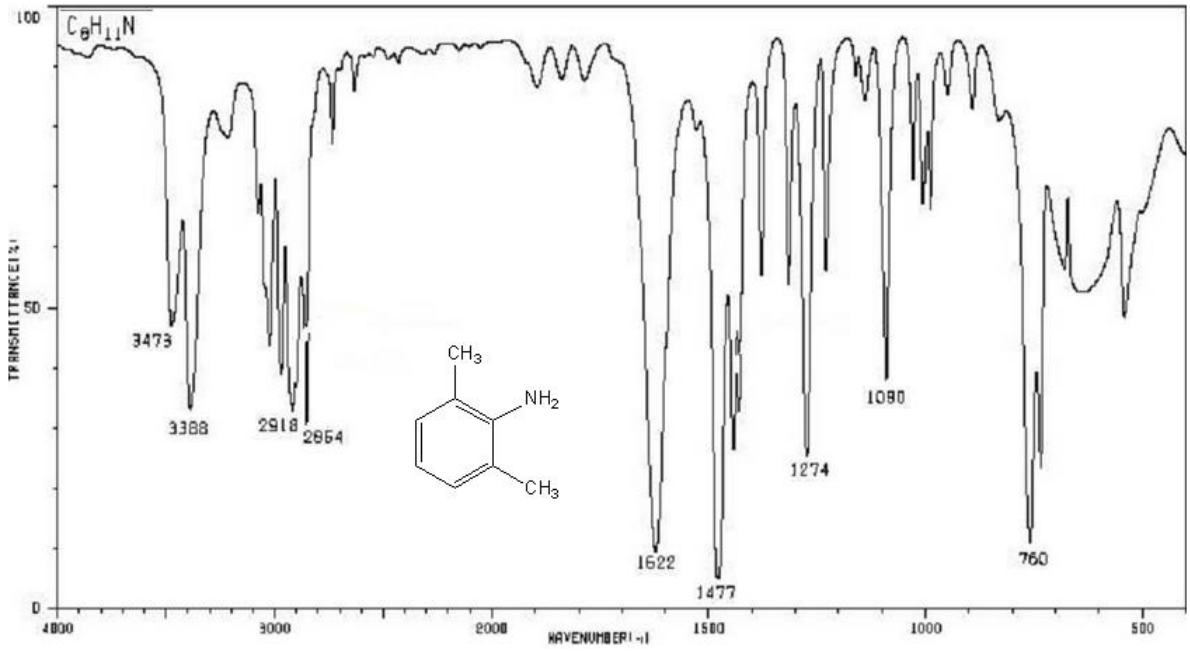
Cool down the mixture in an ice bath for a few minutes, and collect the product on a Büchner funnel. Rinse the solid with small portions of water until acetic acid odor is gone, and dry it by pressing and drawing air through the filter cake on the funnel for about 15 min. Transfer the product to a filter paper and let it air-dry. Weight the product, calculate the percentage yield and measure the m.p. (lit. m.p. 145–146 ^oC).

Thin layer chromatography (TLC):

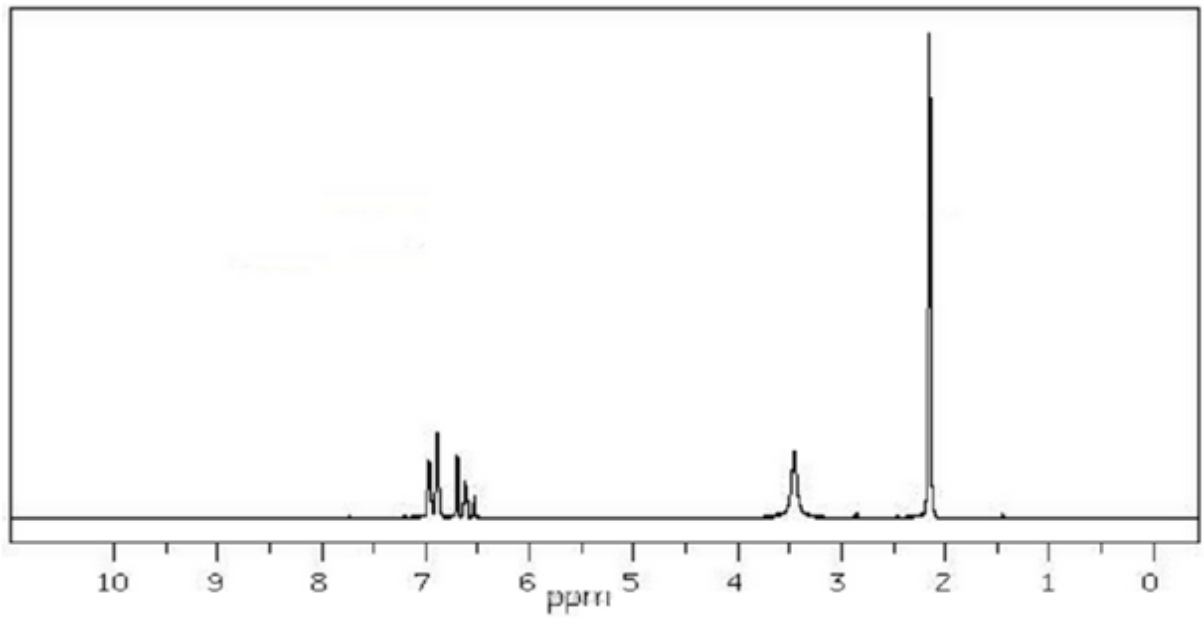
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with hexane/ethyl acetate (9.5:0.5). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

SPECTRA

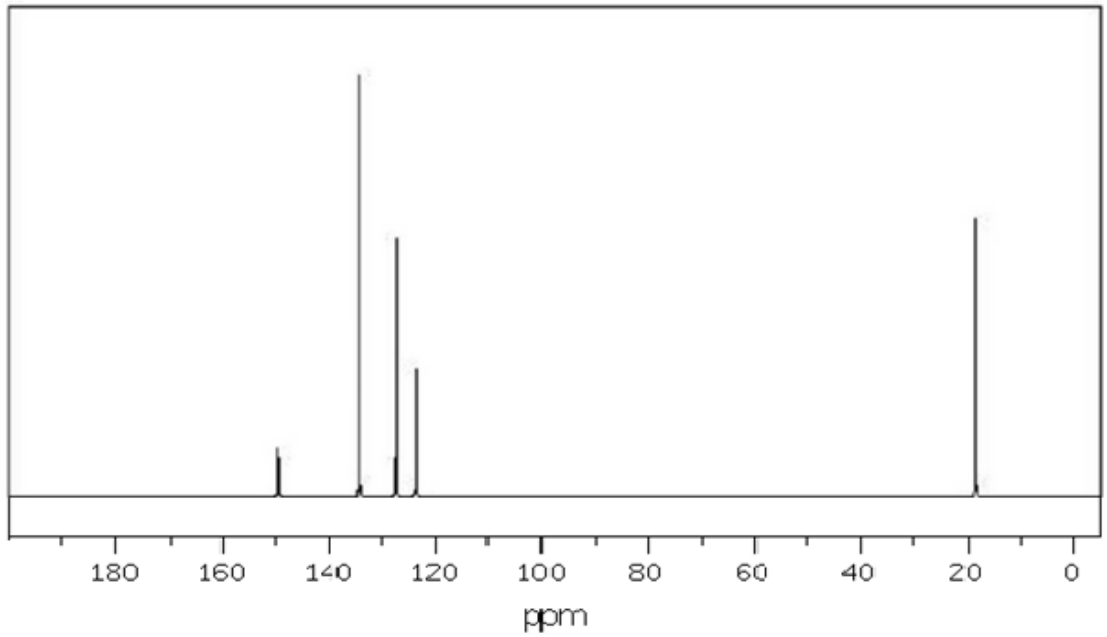
a) FT-IR spectrum of 2,6-dimethylaniline (liquid film).



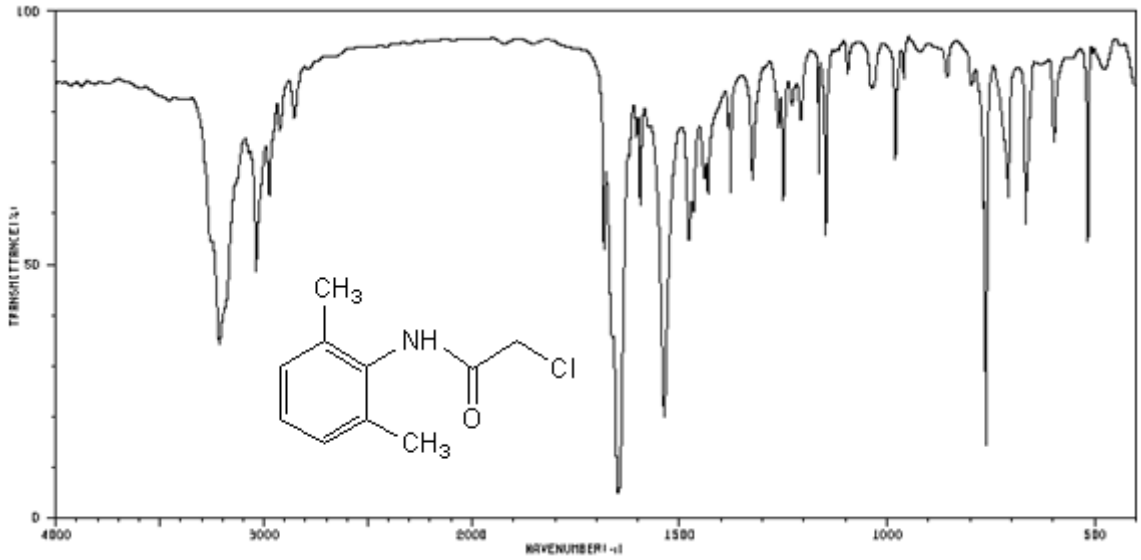
b) ^{1}H NMR spectrum of 2,6-dimethylaniline in $CDCl_3$.



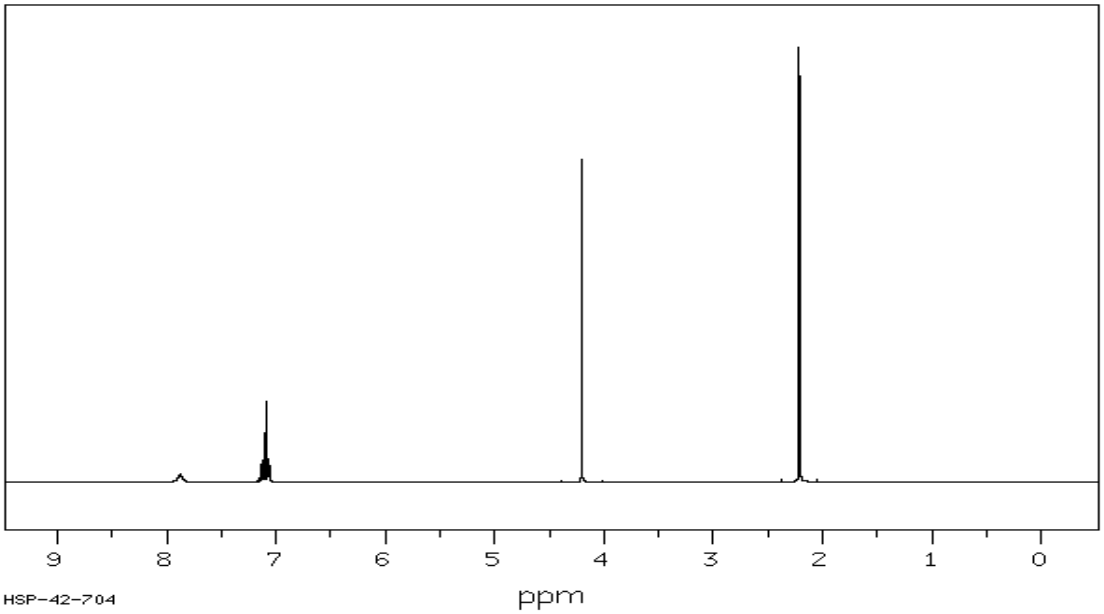
c) ^{13}C NMR spectrum of 2,6-dimethylaniline in $CDCl_3$.



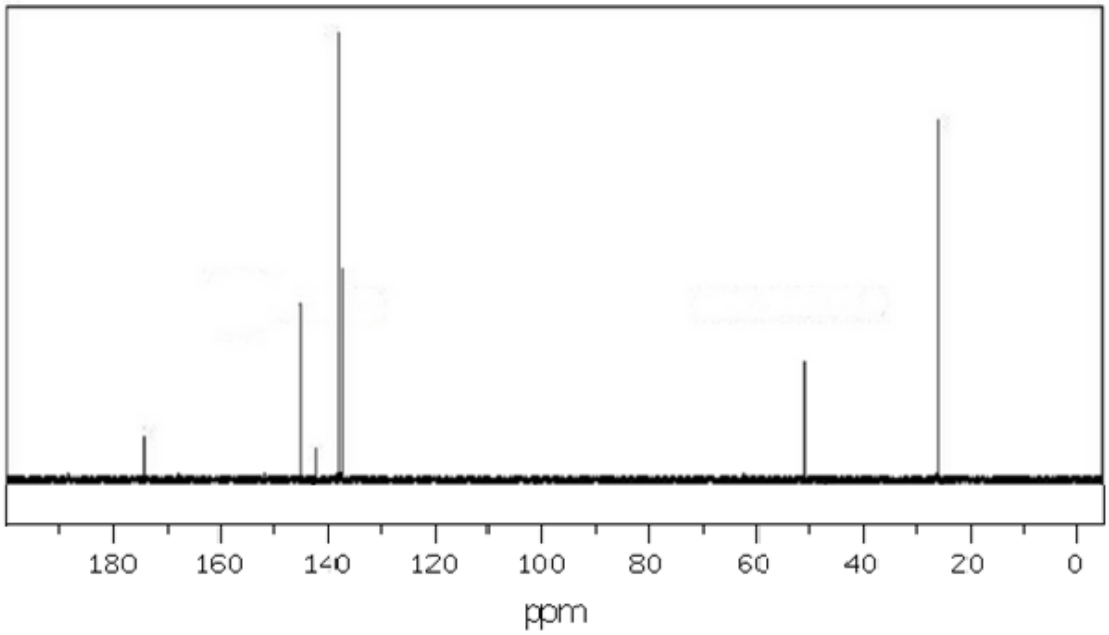
d) FT-IR spectrum of 2−chloro-2,6-dimethylacetanilide in KBr disc.



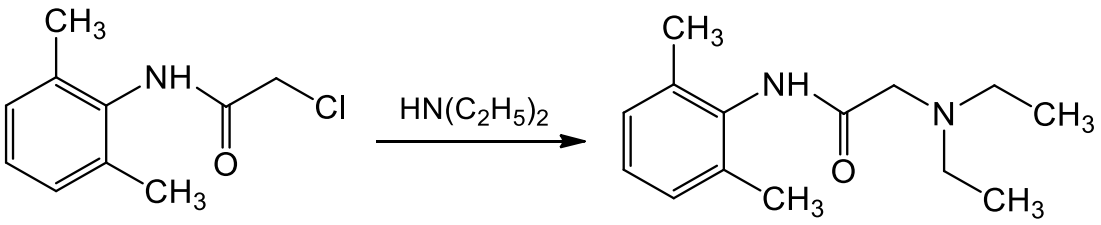
e) ^{1}H NMR spectrum of 2–chloro-2,6-dimethylacetanilide in $CDCl_3$.



f) ^{13}C NMR spectrum of 2–chloro-2,6-dimethylacetanilide in $CDCl_3$.



STEP 2 2 DIETHYLAMINO-2,6-DIMETHYL-ACETANILIDE (LIDOCAINE**)**



Reagents:

2-chloro-2,6-dimethylacetanilide	0.3 g
toluene	4.5 mL
diethylamine	0.42 mL
diethyl ether	20 mL
pH papers	

Glassware:

round-bottom flask 10 mL
reflux condenser
stirrer and heating mantel
graduated pipette
filtering flask with Büchner funnel
separatory funnel 100 mL
Erlenmeyer flask 125 mL
graduated cylinder 25 mL
funnel
Petri dish

In a 10 mL round-bottom flask, place 0.3 g of obtained 2-chloro-2,6-dimethylacetanilide, 4.5 mL of toluene and a stirring bar. Add 0.42 mL of diethylamine to the reaction mixture. Attach a reflux condenser and reflux vigorously for 90 minutes. Then cool down the mixture and store until the next lab period.

Dissolve the formed solid under reflux. Cool the mixture and filter out the crystals formed on a funnel and collect the filtrate. If you do not observe any precipitate, just transfer the filtrate to separatory funnel and wash with water (2 x 5 mL) and extract with dil. HCl (1:5, 3 x 5 mL). Combine acid extracts, made them strong alkaline with 30% KOH (ca. 5 mL). Cool in ice, dark-yellow lidocaine separates. Filter the crystals and extract aqueous phase with *n*-hexane (2 x 10 mL). Combine extracts and crude crystals which dissolve and dry above anh. K_2CO_3, filter the drying agent using cotton tipped glass funnel. Add decolorizing carbon and heat under reflux. Cool down, filter out the carbon and concentrate to approx. 3 mL. Lidocaine crystallizes as colorless crystals. Filter the crystals and dry them on air.

Weigh the product, calculate the percentage yield and measure the m (lit. m.p. 68–69 °C).

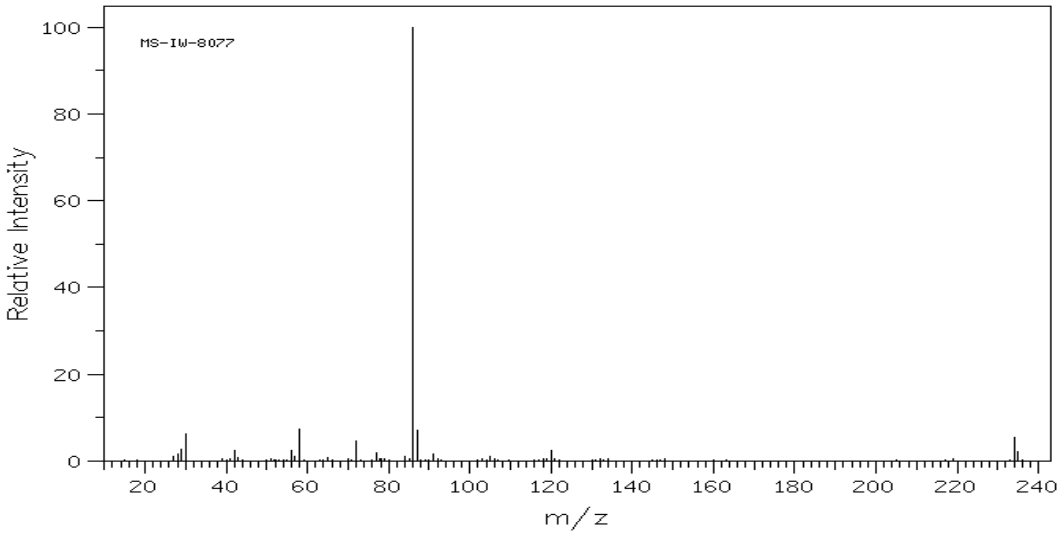
Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with *n*-hexane/ethyl acetate (9.5:0.5). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

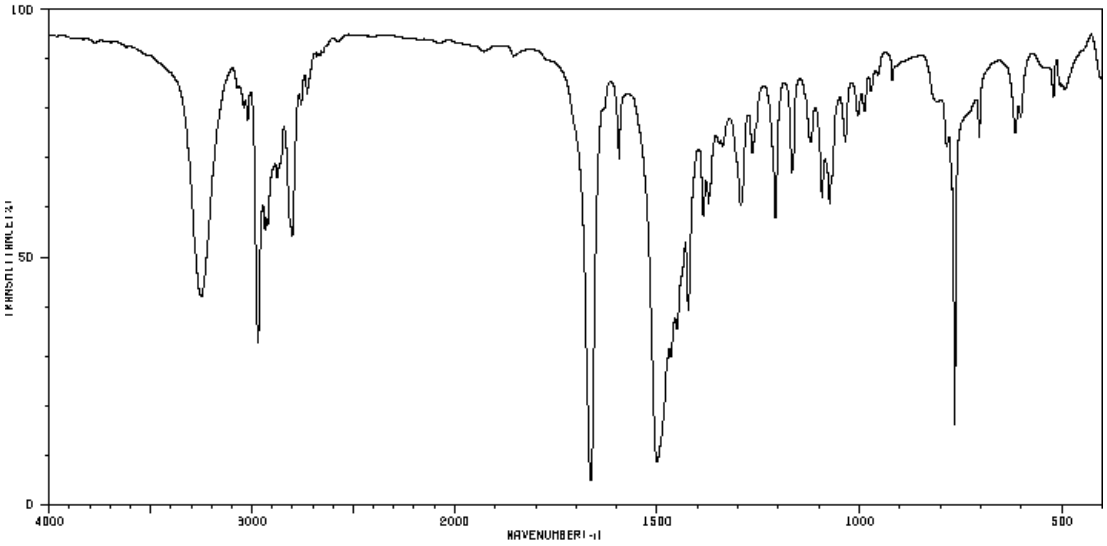
The crude lidocaine is reconverted to the crystalline salt, lidocaine hydrogen sulfate, by dissolving it in diethyl ether (10 mL of solvent per g of solute), and then adding a solution of 2 mL of 2.2 M H_2SO_4 in ethanol per g of solute. Mix the solutions thoroughly and scratch at the air-liquid interface to induce crystallization. Dilute the mixture with an equal volume of acetone to facilitate filtration. Isolate the precipitated salt by vacuum filtration. Rinse the product with acetone and then air-dry. Weight the product, calculate the percentage yield and measure the m.p. (lit. m.p. 210–212 °C).

SPECTRA

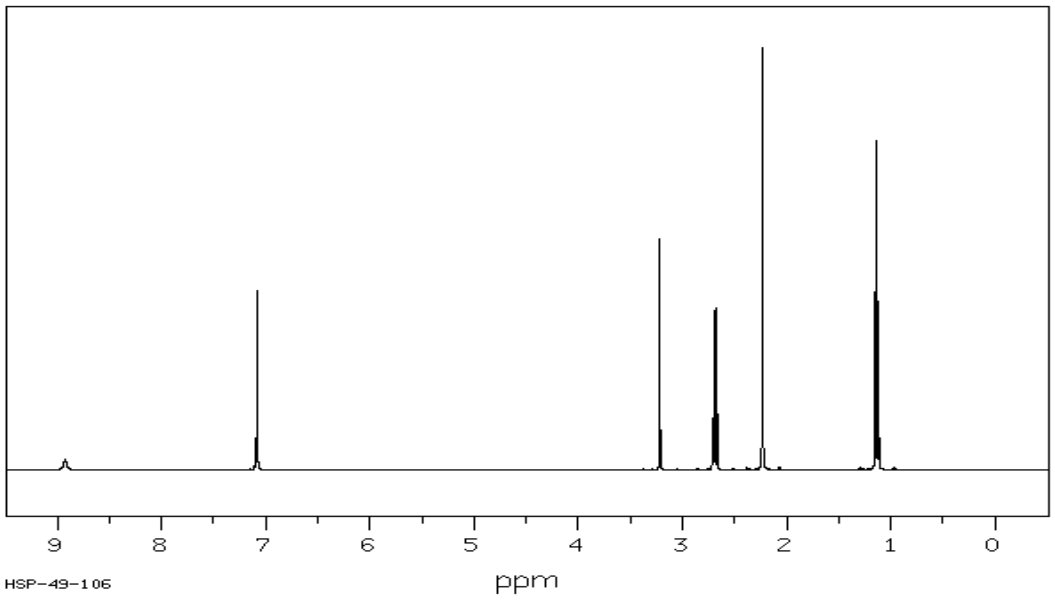
a) MS spectrum of lidocaine.



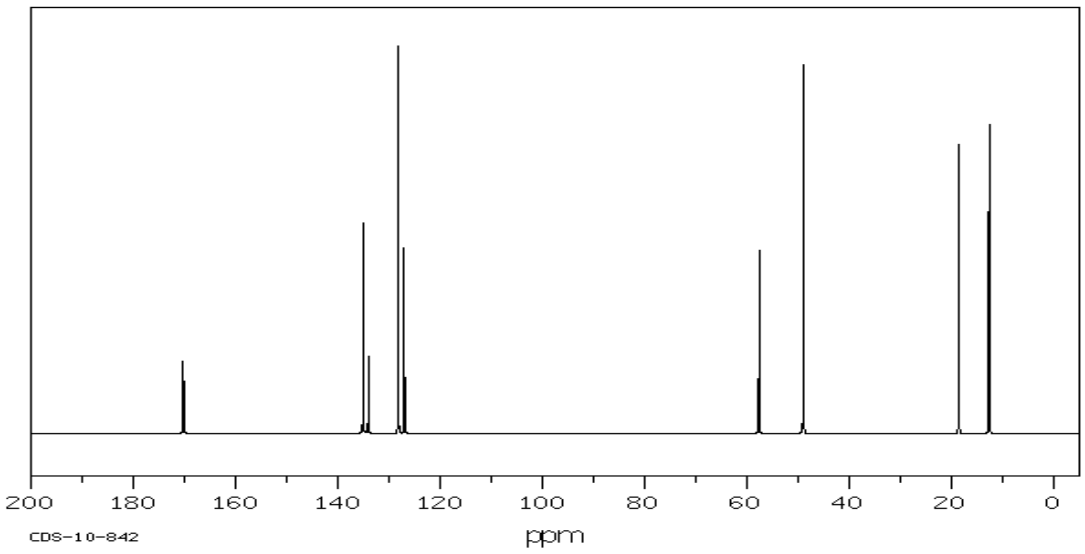
b) FT-IR spectrum of lidocaine in KBr disc.



c) ^{1}H NMR spectrum of lidocaine in $CDCl_3$.



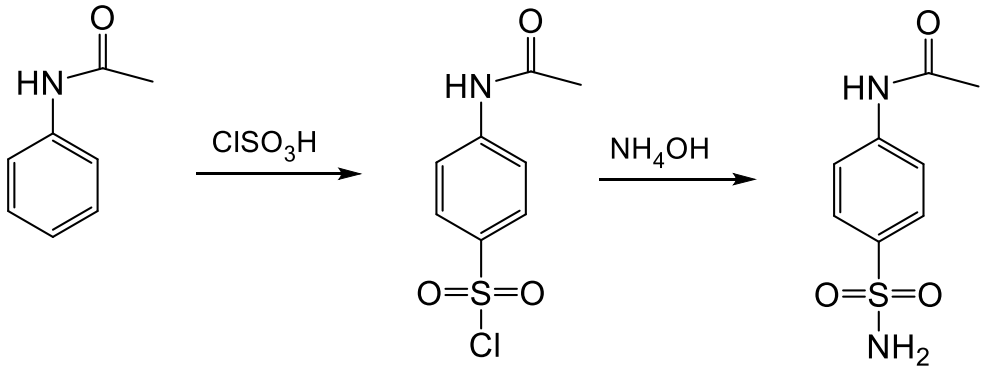
d) ^{13}C NMR spectrum of lidocaine in $CDCl_3$.



21. SULFANILAMIDE (4-AMINOBENZENESULFONAMIDE)

(2 step synthesis)

STEP 1 4-ACETAMIDOBENZENESULFONAMIDE



Reagents:

acetanilide	2.0 g
chlorosulfonic acid	5 mL
12.5% aq. ammonia (ammonium hydroxide)	10 mL

Instrumentation and glassware:

one-necked round-bottom flask 50 mL
dropping funnel
tubing adapter
graduated cylinder
beaker
stirring hotplate
water bath
stirring rod
filtering flask with Büchner funnel
litmus paper (pH paper)

Place 2.0 g of dry acetanilide in a clean and dry 50 mL one-necked round-bottom flask fitted with drying tube. Heat the flask with acetanilide in an oil bath (120–130 ºC) until all of the substrates are completely melted (Note 1).

Remove the oil bath and dry the external surface of the flask with towel paper. After cooling to room temperature, put the flask into an ice-water bath. Equip the flask with a magnetic stirring bar and dropping funnel with pressure equalizing arm and tubing adapter (HCl will be evolved during the reaction).

Then, measure 5 mL of chlorosulfonic acid (Note 2) in a graduated cylinder and transfer it to the dropping funnel. Put the reaction flask in a cold-water bath (15–20 ºC), and next add the chlorosulfonic acid rapidly all at once with stirring, keeping the reaction flask in the cooling bath

(Note 3). After the acetanilide is mostly dissolved, remove the cooling bath and allow the solution to warm to room temperature with continuous stirring.

Heat the reaction mixture in a hot water bath at 70–80 ºC for about 20 minutes to complete the reaction. After cooling the reaction mixture, carefully pour it into 100 mL beaker containing 50 g of crushed ice (Note 4). Stir the ice slurry using stirring rod to prevent formation of large lumps when the product precipitates. Wait until ice is completely melted and collect the precipitate by vacuum filtration on Büchner funnel, wash with 15 mL portions of cold water until the filtrate tests neutral to litmus paper and squeeze the precipitated solid on a filter with stopcock.

Transfer the crude 4-acetamidobenzenesulfonyl chloride to the 50 mL one-necked round-bottom flask equipped with a magnetic stir bar and reflux condenser, and add 10 mL of 12.5% aqueous ammonia (ammonium hydroxide) (Note 5). Heat the resulting thick suspension in a hot water bath at 80–90 ºC for about 30 minutes with stirring until solid is mostly dissolved. Cool the mixture in an ice-water bath and collect the product (very small white needle-like crystals) by vacuum filtration, wash 4 times with approx. 10 mL of cold ice water and dry on air at room temperature. Weigh the product, calculate the yield and measure the m.p. (lit. m.p. 214–216 ºC).

Please note:

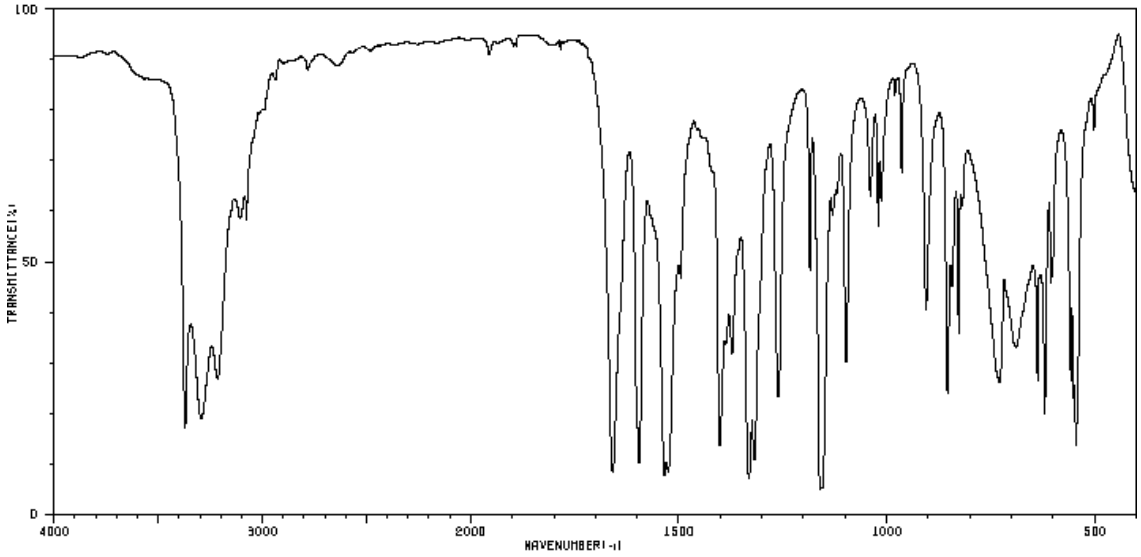
1. Melting point of acetanilide is 115 ºC.
2. Caution! Work under fume hood. Wear gloves and googles! Glassware must be dry because chlorosulfonic acid react violently with water.
3. The temperature must not exceed 25 ºC.
4. Pour the reaction solution over the ice slowly and carefully to avoid splattering.
5. A vigorous reaction may occur if the crude starting material was not previously washed enough to remove strong acid impurities. 12.5% aqueous ammonia is prepared from 25% ammonia.

<u>Thin layer chromatography (TLC):</u>

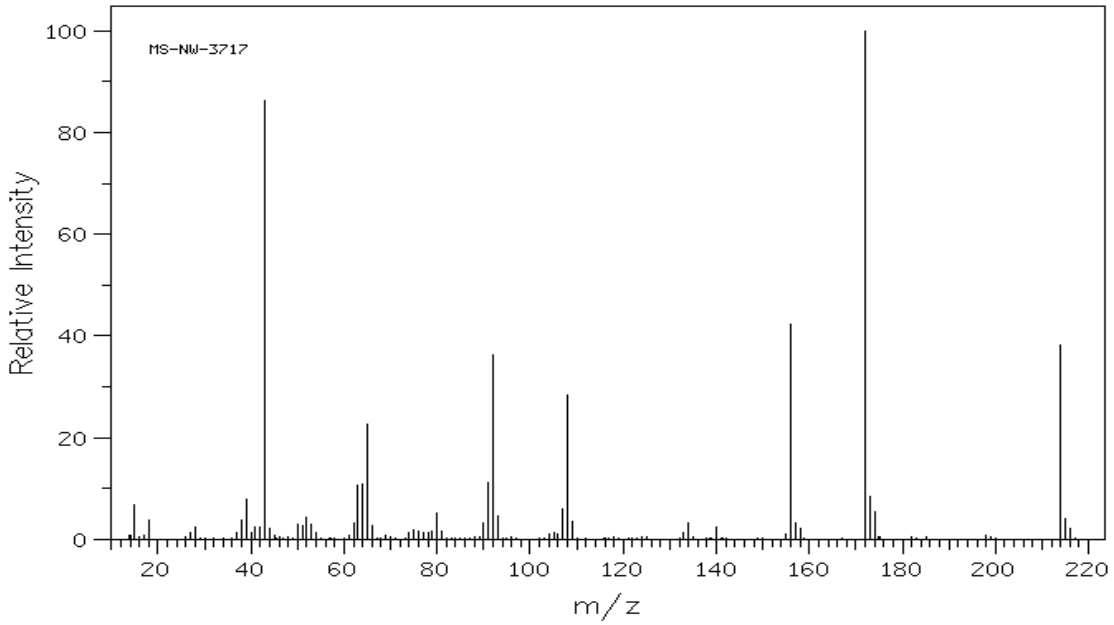
Apply the substrate and product (as a solution in chloroform) onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with ethyl acetate/*n*-hexane (1:1). Remove the plate and allow the solvent to evaporate. The spot of 4-acetamidobenzenesulfonamide is visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

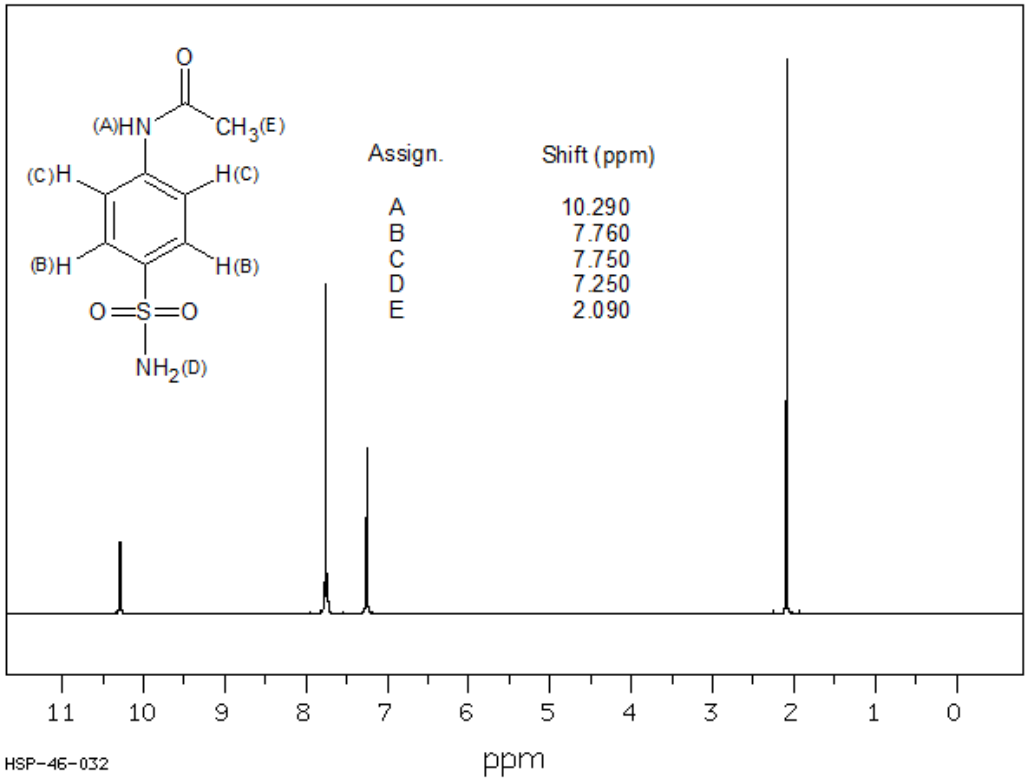
a) FT-IR spectrum of 4-acetamidobenzenesulfonamide in KBr disc.



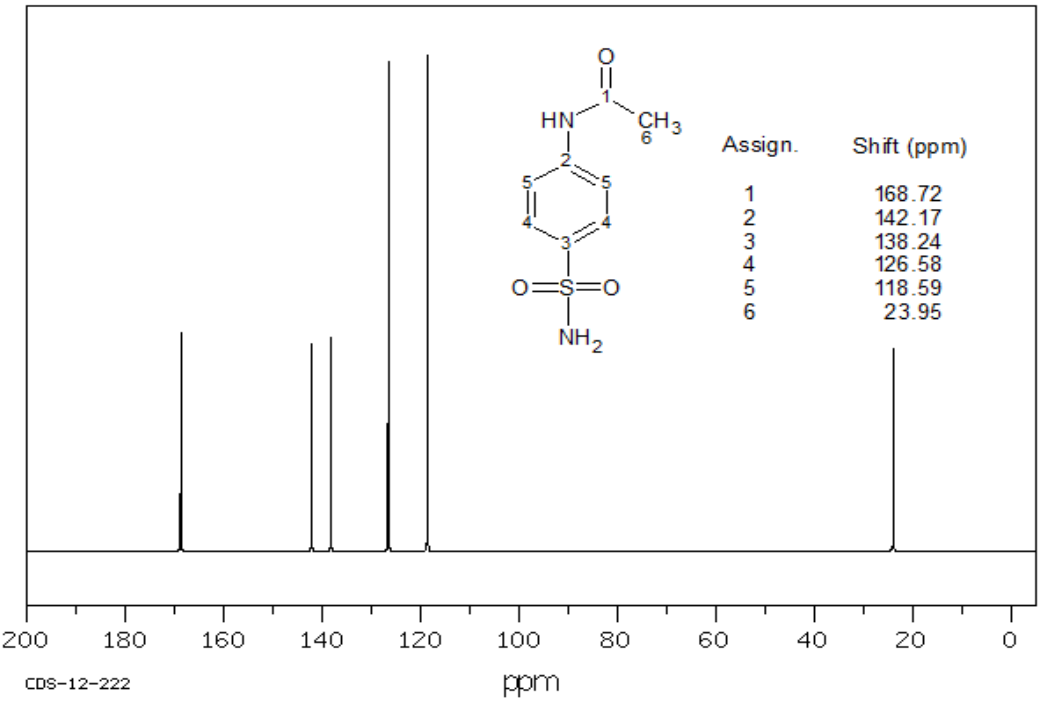
b) EI-MS mass spectrum of 4-acetamidobenzenesulfonamide.



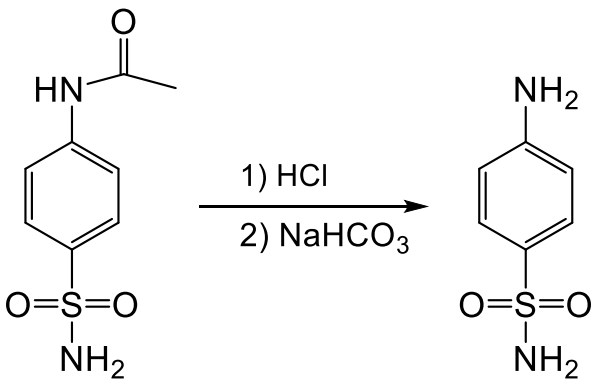
c) ^{1}H NMR spectrum of 4-acetamidobenzenesulfonamide in DMSO-*d*$_6$.



d) ^{13}C NMR spectrum of 4-acetamidobenzenesulfonamide in DMSO-*d*$_6$.



STEP 2 4-AMINOBENZENESULFONAMIDE (SULFANILAMIDE)



Reagents:		**Instrumentation and glassware:**
4-acetamidobenzenesulfonamide	1.5 g	round-bottom flask 50 mL
conc. HCl	3 mL	beaker
$NaHCO_3$	3.0 g	Liebig condenser
		heating mantle
		litmus paper (pH paper)
		filtering flask with Büchner funnel

Place 1.5 g of 4-acetamidobenzenesulfonamide from the previous step in a 50 mL round-bottom flask equipped with a magnetic stir bar. Separately in a beaker dilute the HCl by adding 3 mL concentrated HCl to 6 mL of distilled water. Add prepared dilute HCl solution to the reaction flask with 4-acetamidobenzenesulfonamide fitted with a water condenser and heat at reflux with constant stirring for 45 minutes (the solid should dissolve) and allow the reaction mixture to cool to room temperature. If any solid appears upon cooling, reheat the mixture at reflux for another 15 minutes. After cooling transfer the reaction mixture to the 250 mL beaker and neutralize by slow addition of previously prepared saturated $NaHCO_3$ solution with stirring until it tests slightly alkaline to litmus paper. A precipitation should begin during neutralization. Cool the mixture in an ice bath to complete the precipitation of product (Note 1) Collect the product by vacuum filtration, wash with a small amount of cold water. Recrystallize the sulfanilamide from minimum amount of water.

Weigh the product, calculate the yield and measure the m.p. (lit. 161-162 ^{o}C).

Please note:

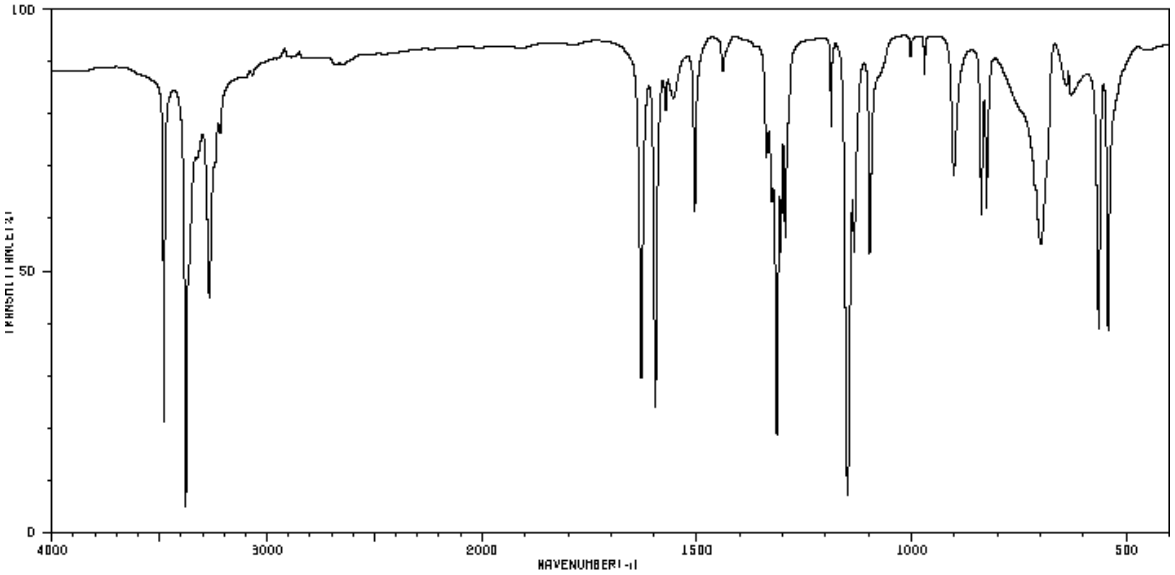
It may be necessary to gently scratch the inside bottom of the beaker with a glass rod to induce crystallization.

Thin layer chromatography (TLC):

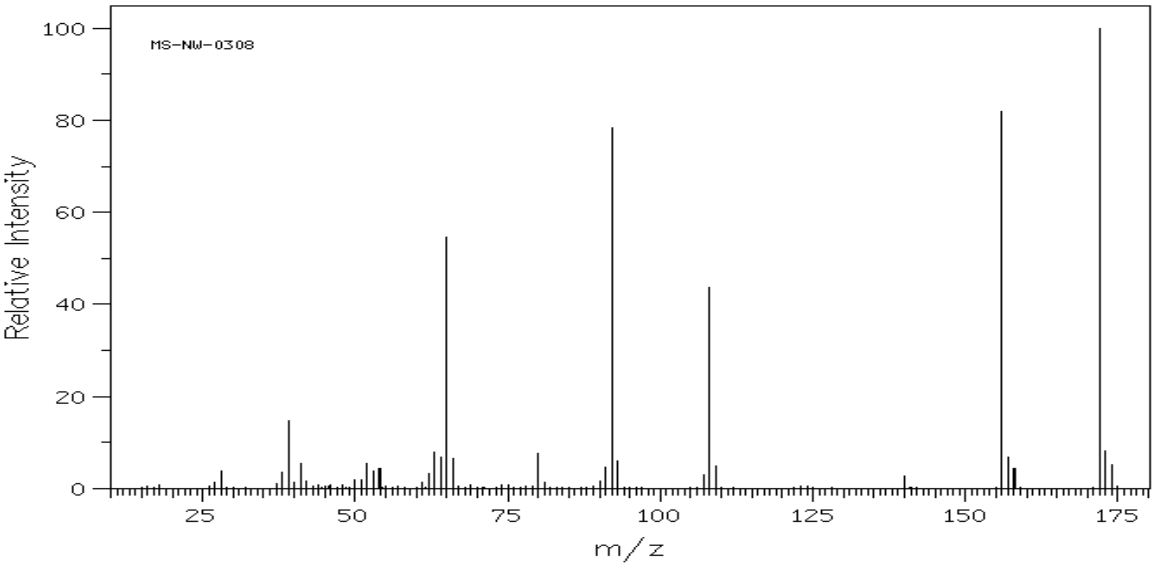
Apply the substrate and product (as a solution in chloroform) onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with ethyl acetate/hexane (1:1). Remove the plate and allow the solvent to evaporate. The spot of sulfanilamide is visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

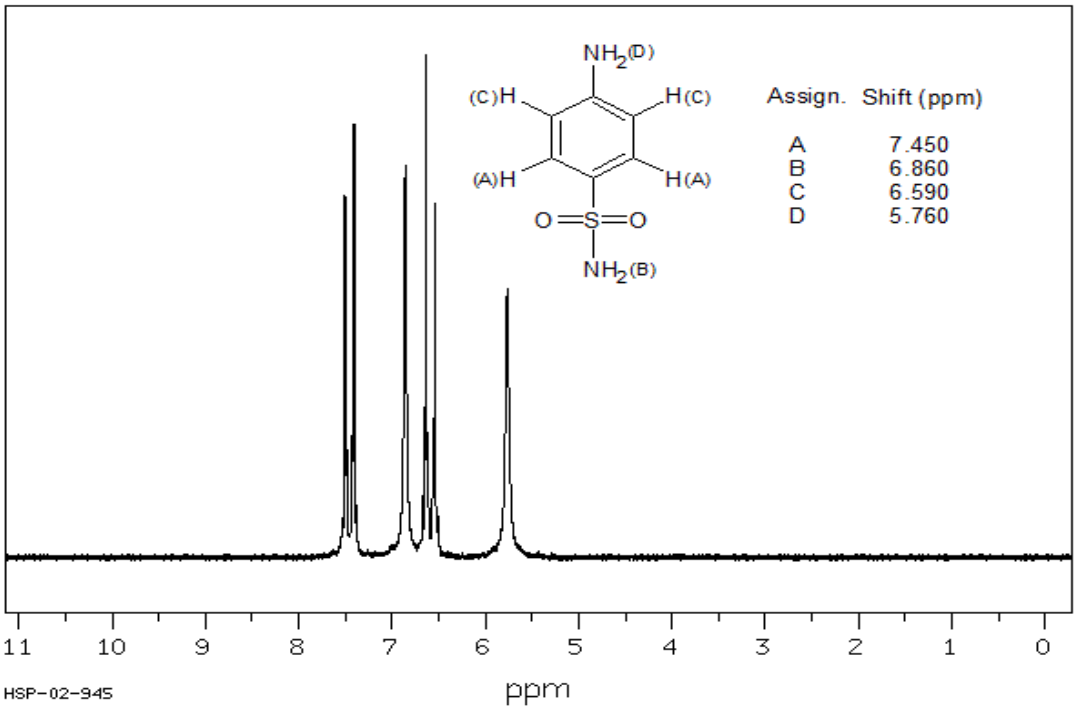
a) FT IR spectrum of sulfanilamide in KBr disc.



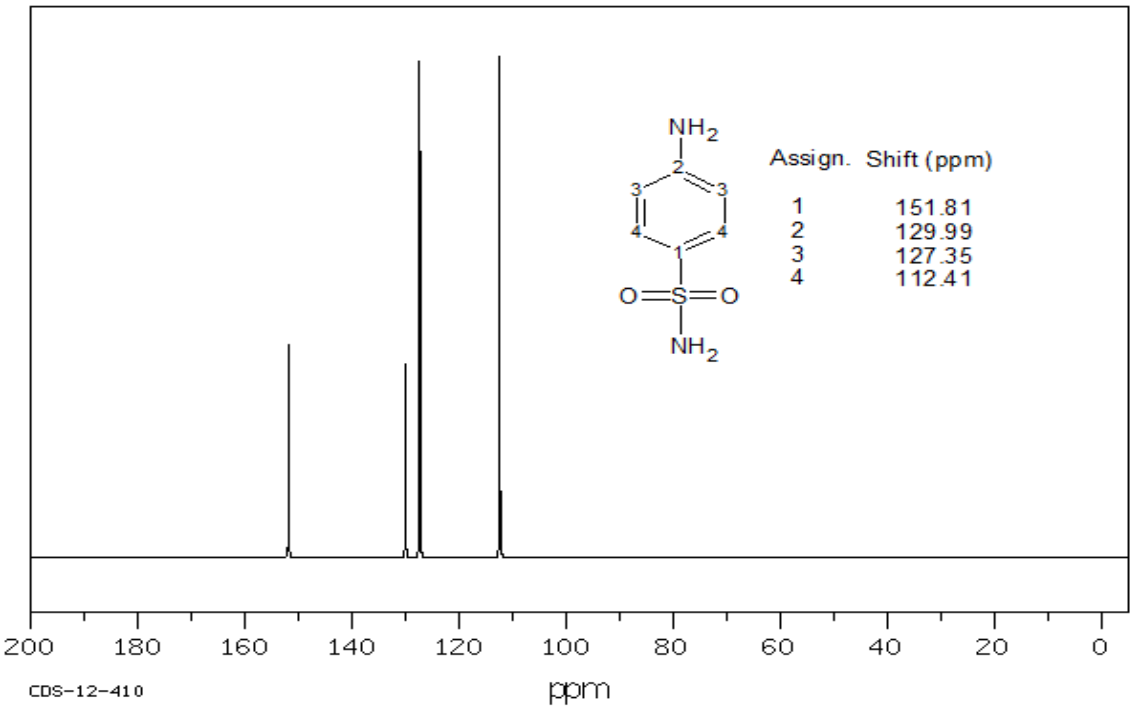
b) EI MS mass spectrum of sulfanilamide.



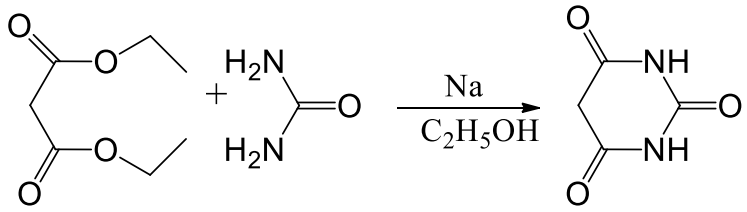
c) ^{1}H NMR spectrum of sulfanilamide in DMSO-d_6 (90 MHz).



d) ^{13}C NMR spectrum of sulfanilamide in DMSO-d_6 (25 MHz).



22. BARBITURIC ACID



Reagents:		**Instrumentation and glassware:**
sodium	1.2 g	round-bottom flask 250 mL
abs. ethanol	50 mL	condenser
diethyl malonate	7.6 mL	filtering flask with Büchner funnel
urea	3.0 g	measuring cylinder
HCl	5 mL	

Place 1.2 g of clean sodium metal into a 250 mL round-bottom flask, fitted with a reflux condenser. Add 25 mL of absolute ethanol in one portion. If the reaction is unduly vigorous, immerse the flask momentarily in ice.

After the sodium has reacted, add 7.6 mL of diethyl malonate. Then, 3.0 g of urea previously dissolved in 25 ml of absolute ethanol (70 ^{o}C) add to the flask. Shake the mixture well, and proceed the reaction under reflux until the white solid appears in the flask.

Quench the reaction by adding 45 mL of hot distilled water (50 ^{o}C) and acidify the mixture with ca. 5 mL of conc. HCl. Filter the resulting mixture (remove the solid staff) and allow to crystallize in the refrigerator for overnight or one week. Filter the formed crystals and wash them with cold water. Then, dry the product in an oven at 90 ^{o}C for 2 hours.

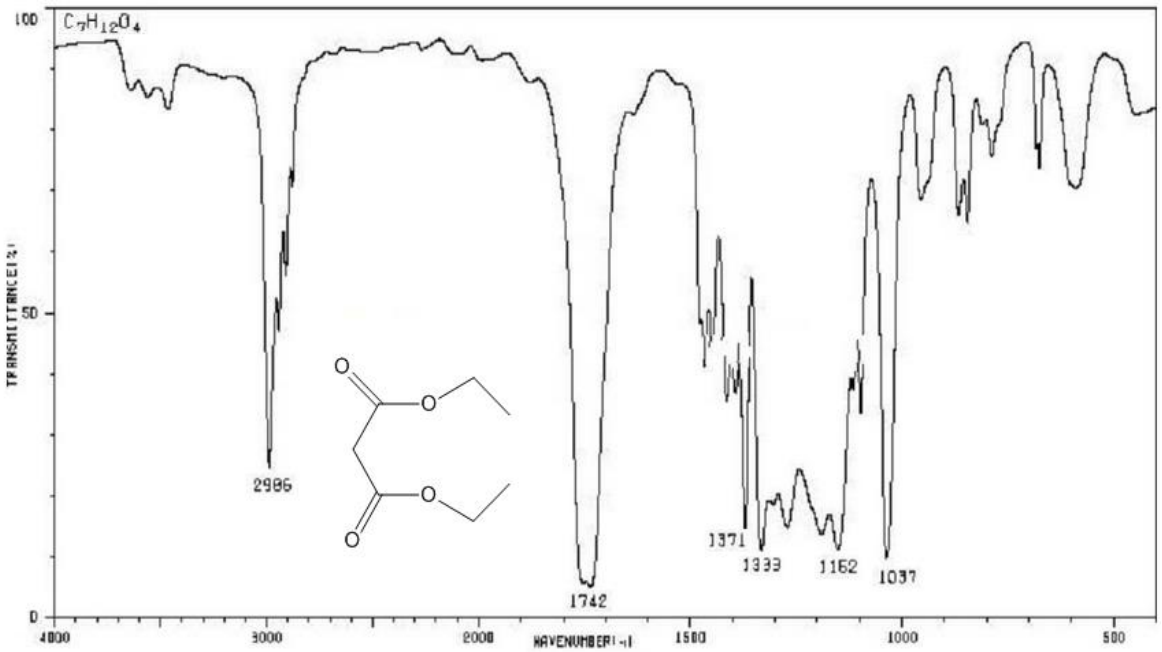
Weigh the product, calculate the yield of barbituric acid and measure the m.p. (lit. melts with decomposition at 245 ^{o}C).

Thin layer chromatography (TLC):

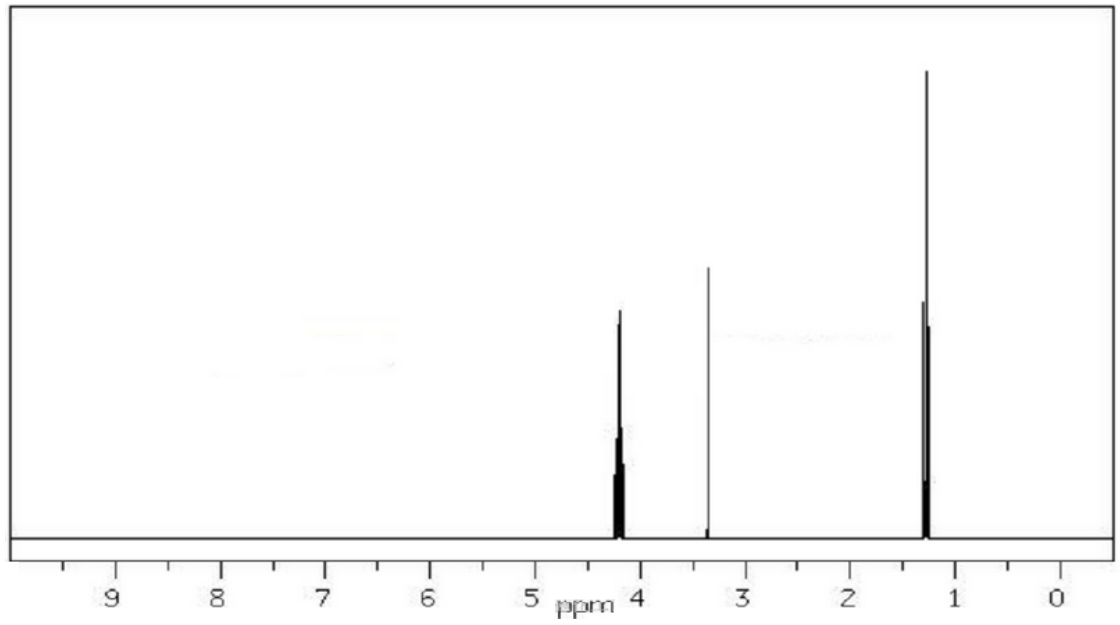
Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with EtOH/CH_2Cl_2 (8:1). Remove the plate and allow the solvent to evaporate. The spot of the product is visible under the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

SPECTRA

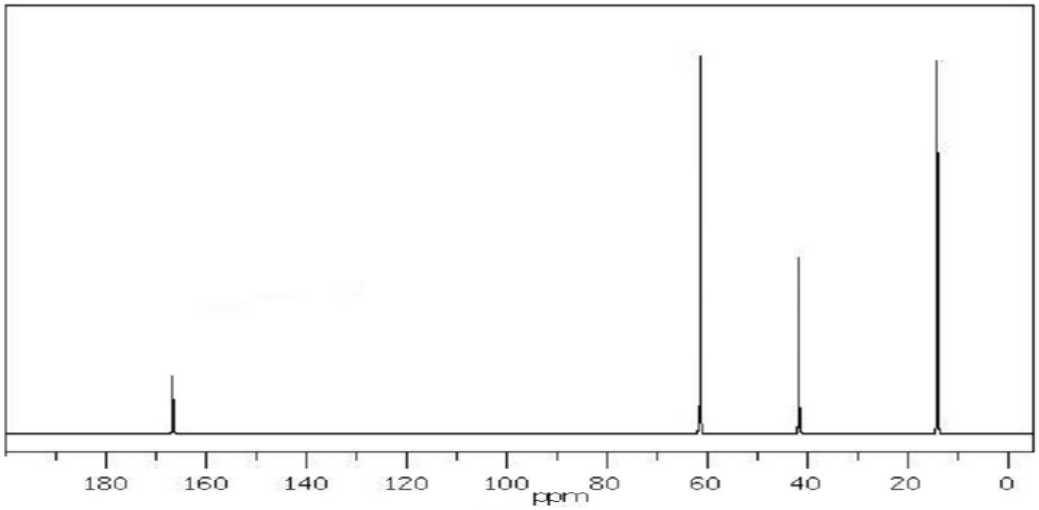
a) FT-IR spectrum of diethyl malonate (liquid).



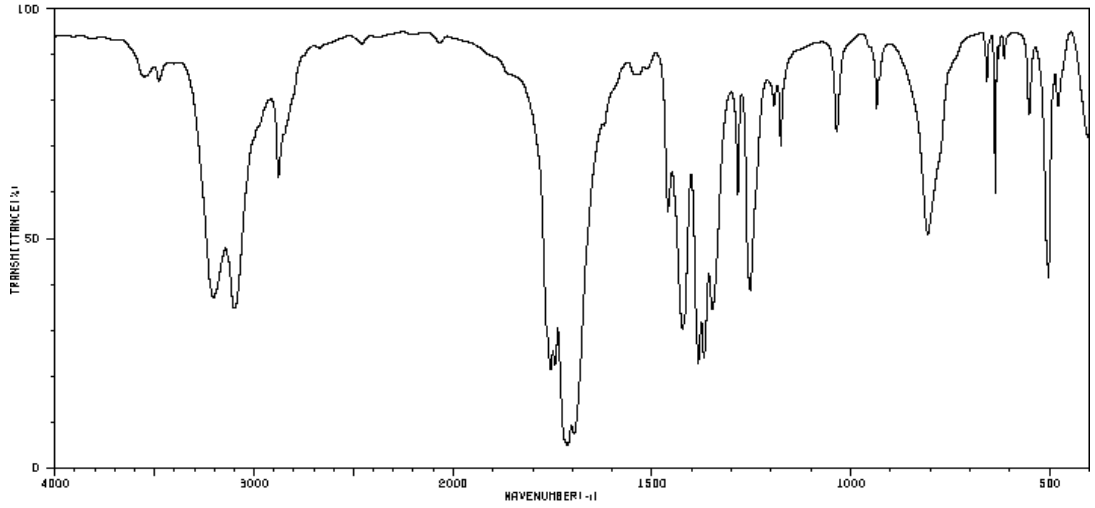
b) ^{1}H NMR spectrum of diethyl malonate in $CDCl_3$.



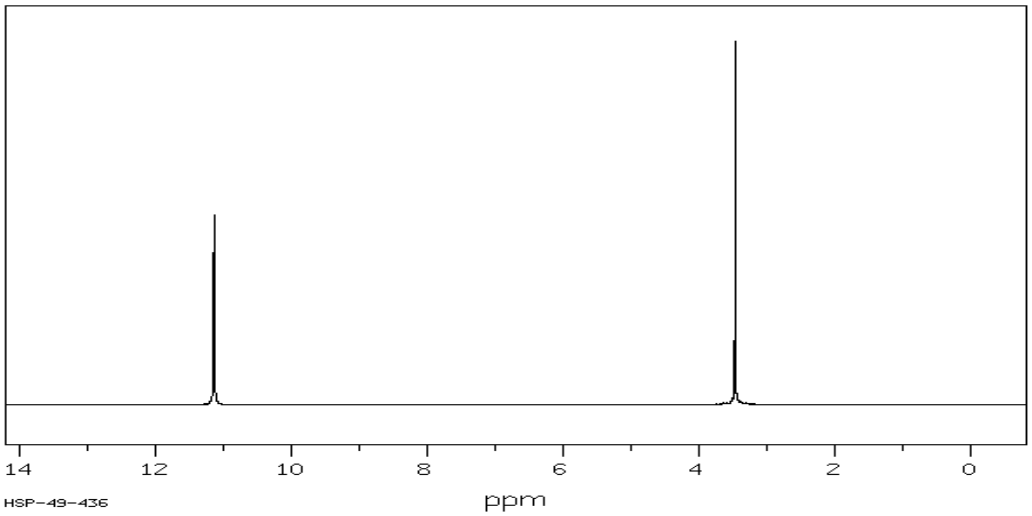
c) ^{13}C NMR spectrum of diethyl malonate in $CDCl_3$.



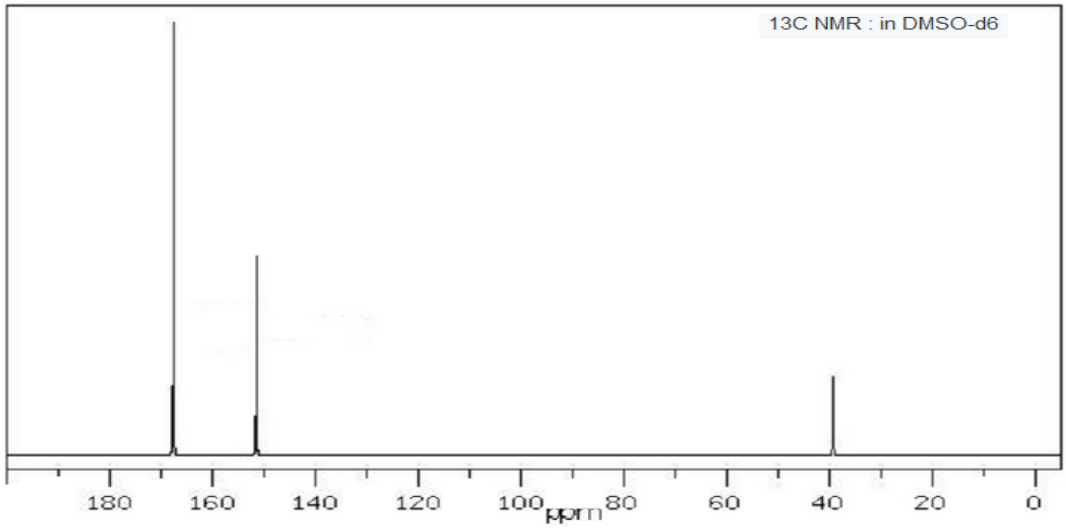
d) FT-IR spectrum of barbituric acid in KBr disc.



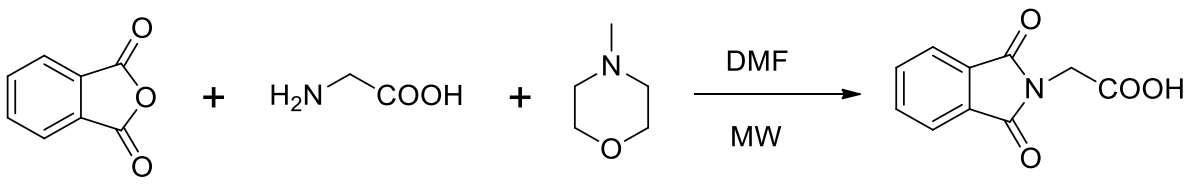
e) ^{1}H NMR spectrum of barbituric acid in DMSO-d_6.



f) ^{13}C NMR spectrum of barbituric acid in DMSO-d_6.



23. *N*-PHTALOYLGLYCINE



Reagents:		**Instrumentation and glassware:**
phthalic anhydride	0.21 g	microwave vial
glycine	0.11 g	filtering flask with Büchner funnel
N,*N*-dimethylformamide	0.5 mL	crystallizing dish
N-methylmorpholine	0.05 mL	glass rod
		ice bath

The mixture of phthalic anhydride (0.21 g) with glycine (0.11 g) ground thoroughly in a mortar, and then transfer to a microwave vial. After the addition of 0.5 mL of *N*,*N*-dimethylformamide followed by 0.05 mL of *N*-methylmorpholine, the mixture shake gently.

Place the closed vial in the microwave oven. The irradiation was carried out for 5 min at a 180°C. After cooling, add 10 mL of water to the mixture. The vial with product place in an ice bath to crystallize the product (about 20 min).

The precipitated *N*-phthaloylglycine filter on a foam funnel or Büchner funnel and recrystallize from 95% ethanol or water. Filter the product, dry and measure melting point and FT-IR. The average yield was 75%, m.p. 192–195 °C.

Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate).

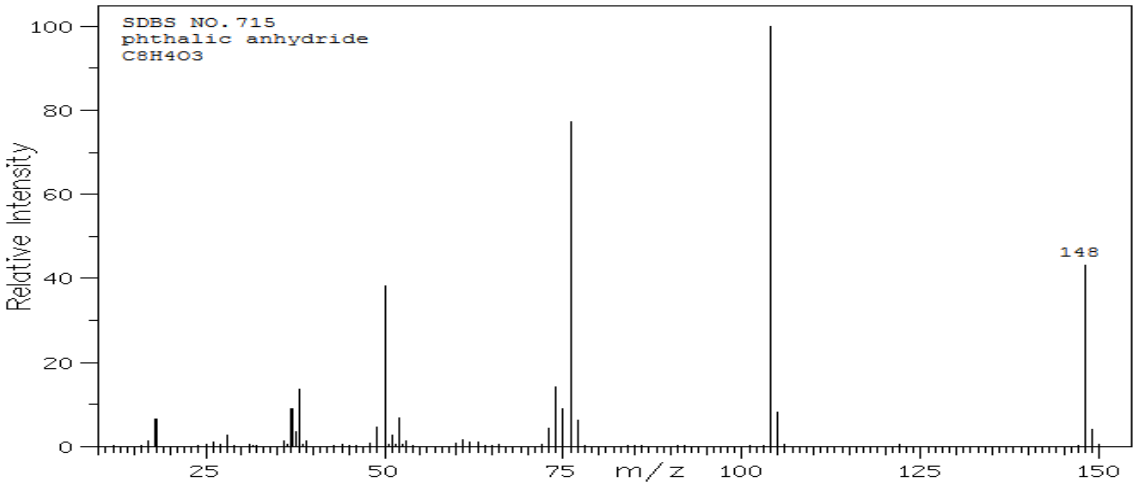
Develop with methanol/water (9:1). Remove the plate and dry using hair-dryer. The spots of the compounds are visible under the UV light.

Please note:

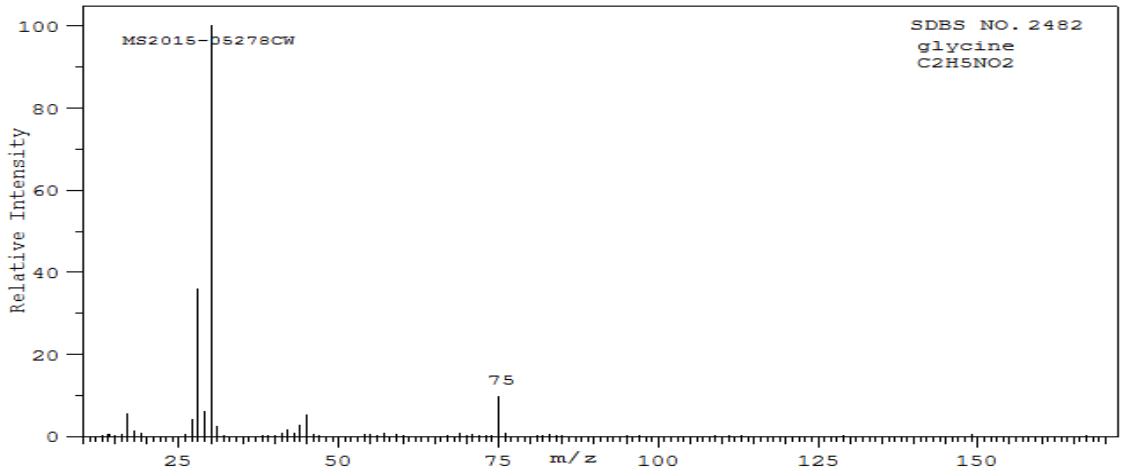
For the reaction in 100 mL a round-bottom flask, add 20 mL xylene and heat under cooler in a microwave oven for 60 min at 130^{o}C.

SPECTRA

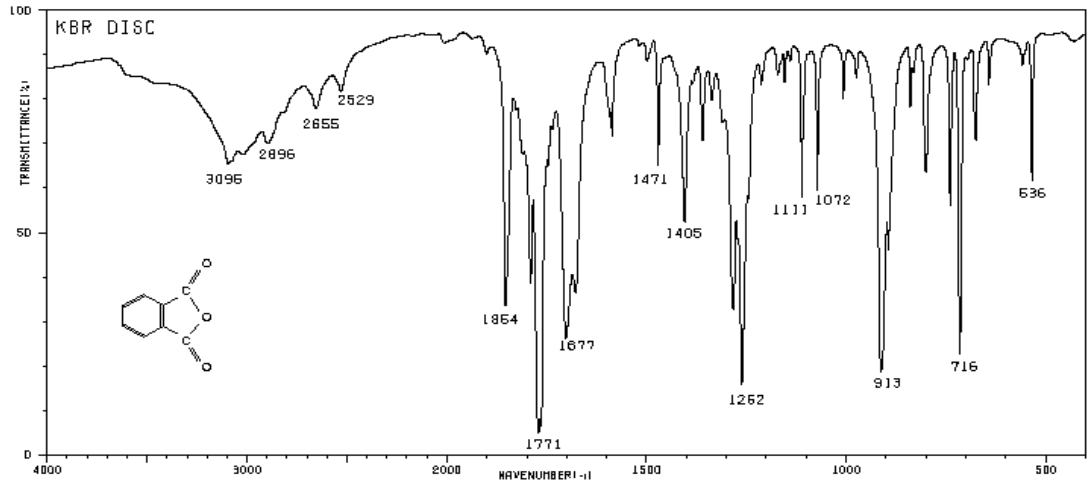
a) EI-MS spectrum of phtalic anhydride.



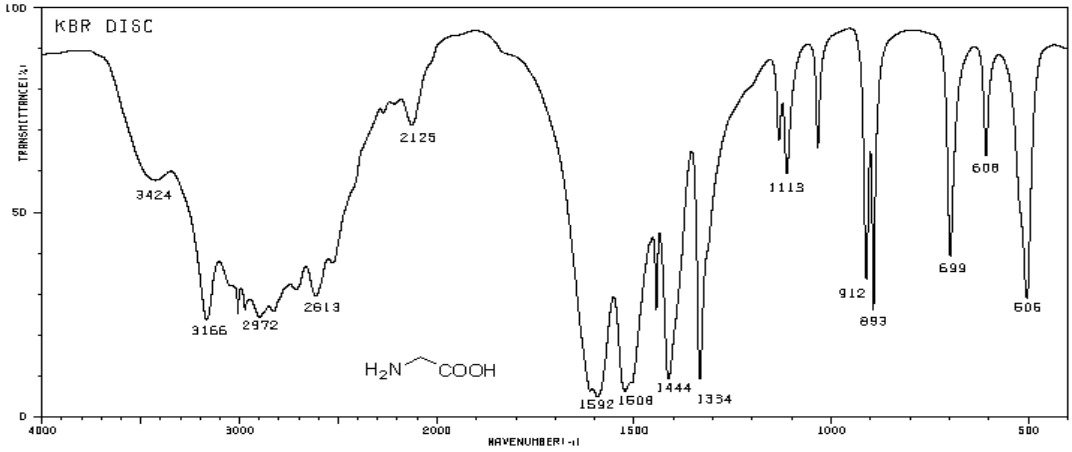
b) EI-MS spectrum of glycine.



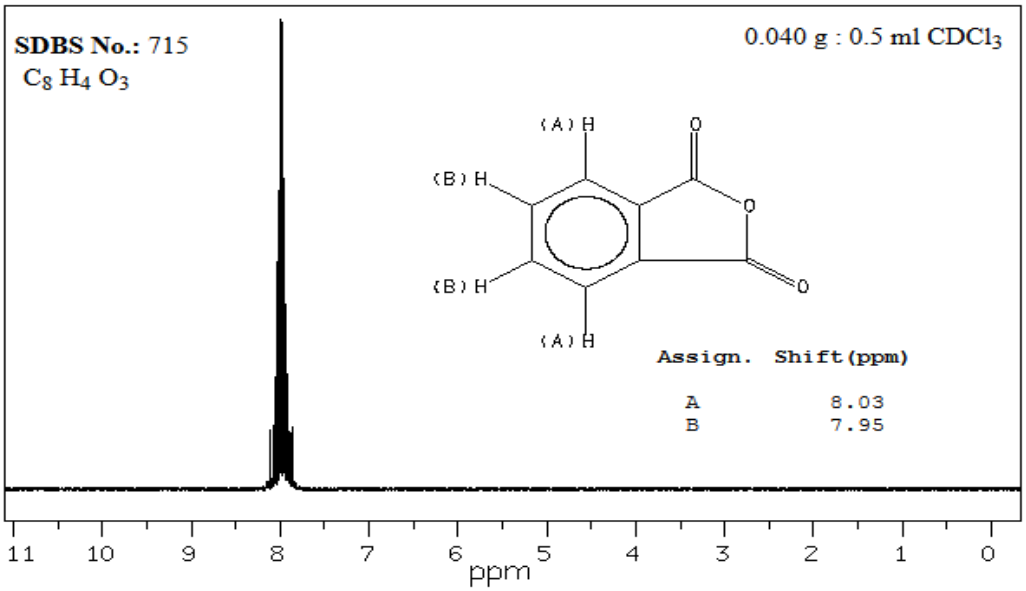
c) FT-IR spectrum of phtalic anhydride.



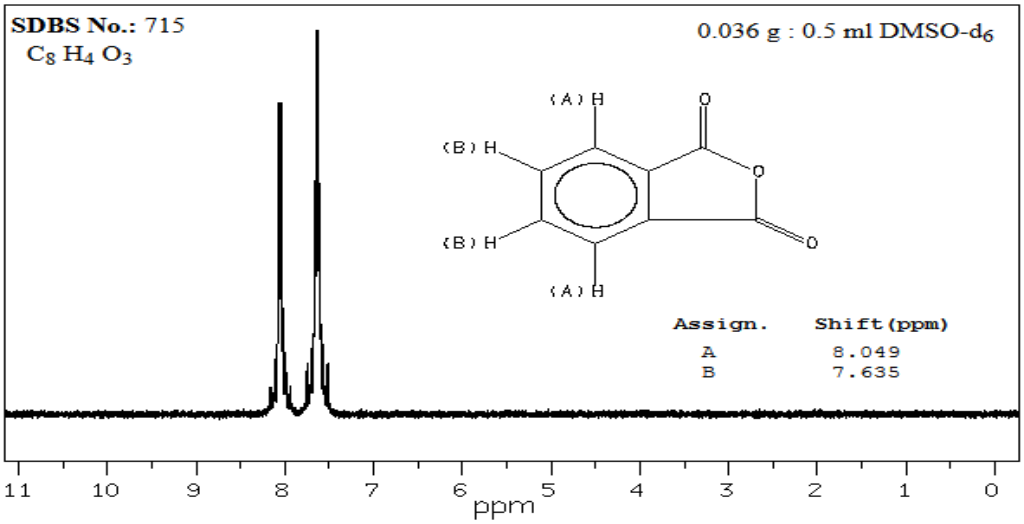
d) FT-IR spectrum of glycine.



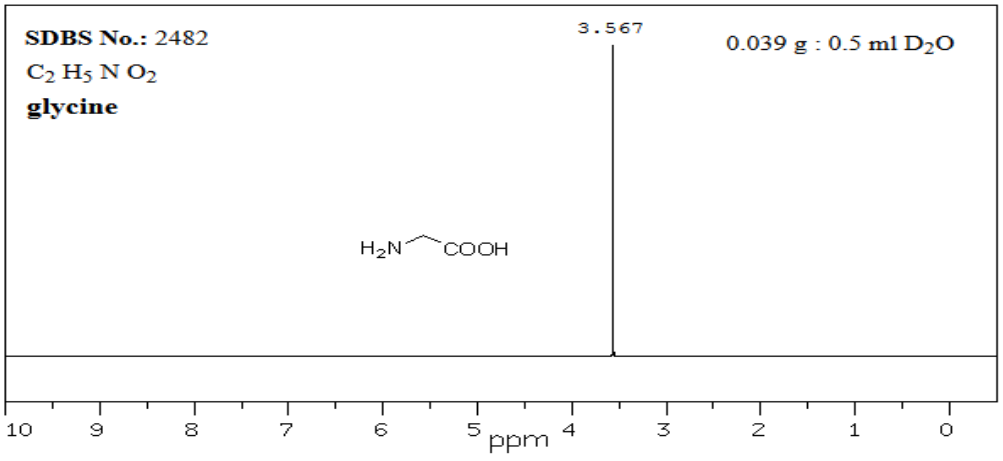
e) ^{1}H NMR spectrum of phtalic anhydride in $CDCl_3$.



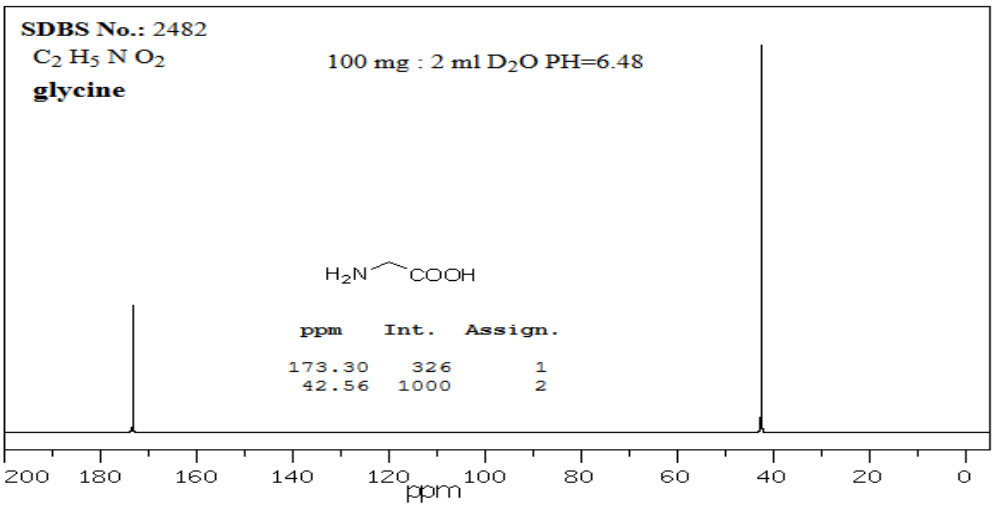
f) ^{1}H NMR spectrum of phtalic anhydride in DMSO-d_6.

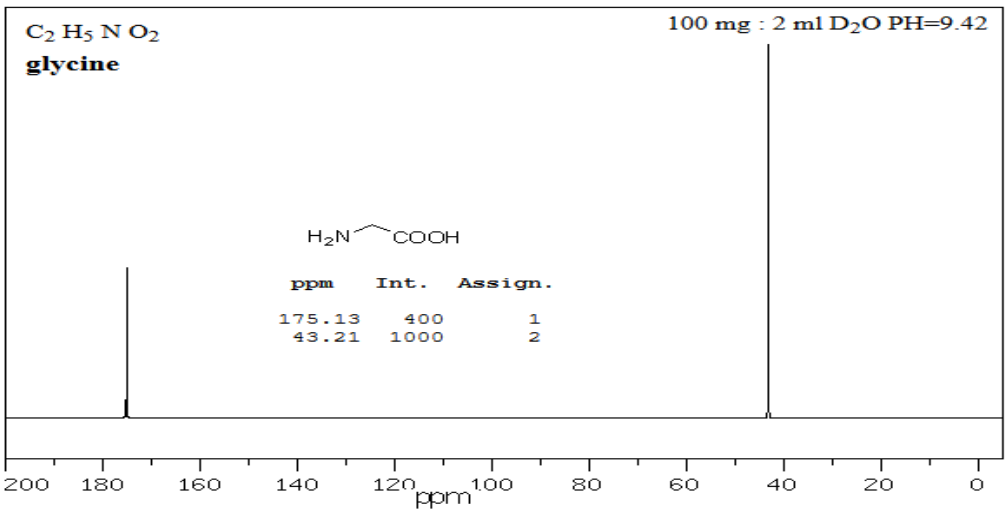


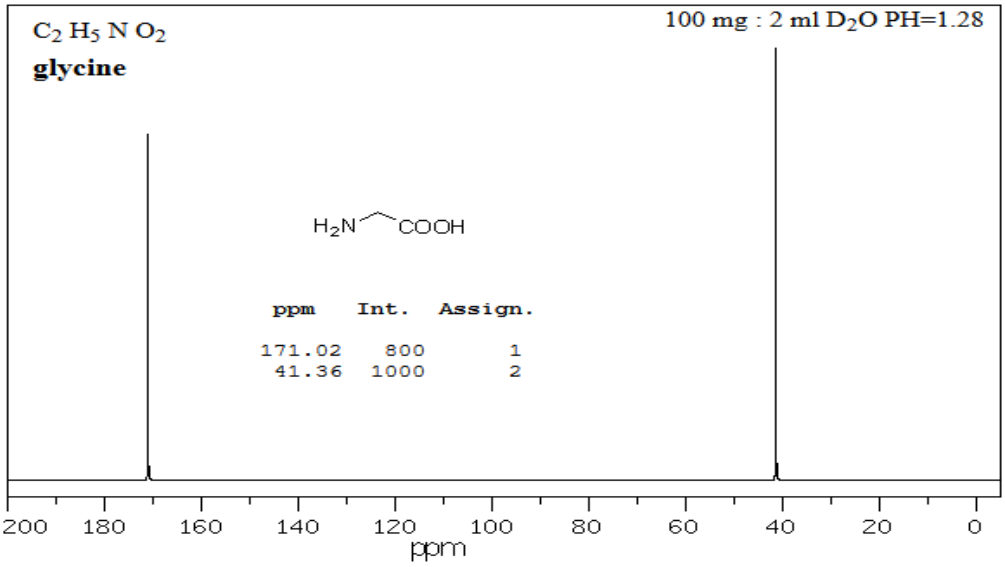
g) ^{1}H NMR spectrum of glycine in D_2O.



h) ^{13}C NMR spectrum of glycine in D_2O in different pH of the solvent.



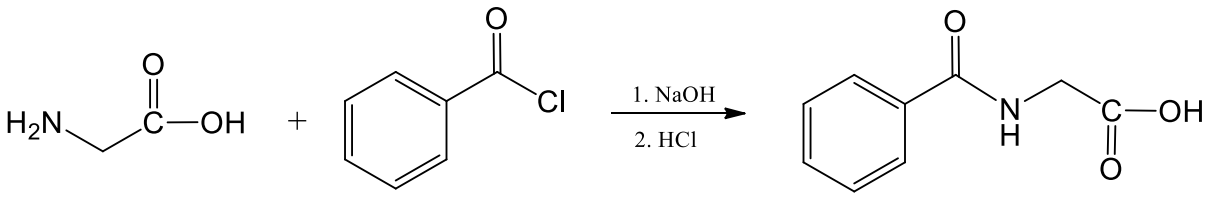




References

Bari S.S., Bose A. K., Chaudhary A.G., Manhas M. S., Raju V. S., Robb A. W.: Solvent free synthesis of N-Sulfonylimines using microwave Irradiation, *J. Chem. Ed*. 1992, 69 (11), 938.

24. BENZOYLGLYCINE (HIPPURIC ACID)



Reagents:		**Instrumentation and glassware:**
		heating mantle
glycine	0.03 mole (2.3 g)	round flask 50 mL
10% NaOH	19 mL	condenser
benzoyl chloride	0.03 mole (3,5 mL)	filtrating flask with Büchner funnel
conc. HCl	5 mL	beaker 50 mL
Congo red paper		glass rod
chloroform	10 mL	magnetic stirrer

In conical flask prepare 10% of sodium hydroxide solution and dissolve in it 0.03 mole of glycine. Add 0.03 mole of benzoyl chloride in 5 portions to the solution. Stopper the vessel and shake vigorously after each addition until all the chloride has reacted. Transfer the solution to a beaker and rinse the conical flask with a little water. Place a few pieces of crushed ice to the solution and add slowly 5 mL of HCl with stirring until the mixture is acid to Congo red paper.

Collect the resulting crystalline precipitate of benzoylglycine, which is contaminated with a little benzoic acid, upon a Büchner funnel, wash with cold water and drain well. Place the solid in a round bottom flask with 10 mL of chloroform and heat under reflux. This process allows to remove the traces of benzoic acid, which may be still present in the obtained crude product. Then, cool down the mixture and filter the product on Büchner funnel, and dry on air on Petri dish.

Weight the product, calculate the percentage yield and measure the m.p. (lit. 186-187 ^{o}C).

Thin layer chromatography (TLC):

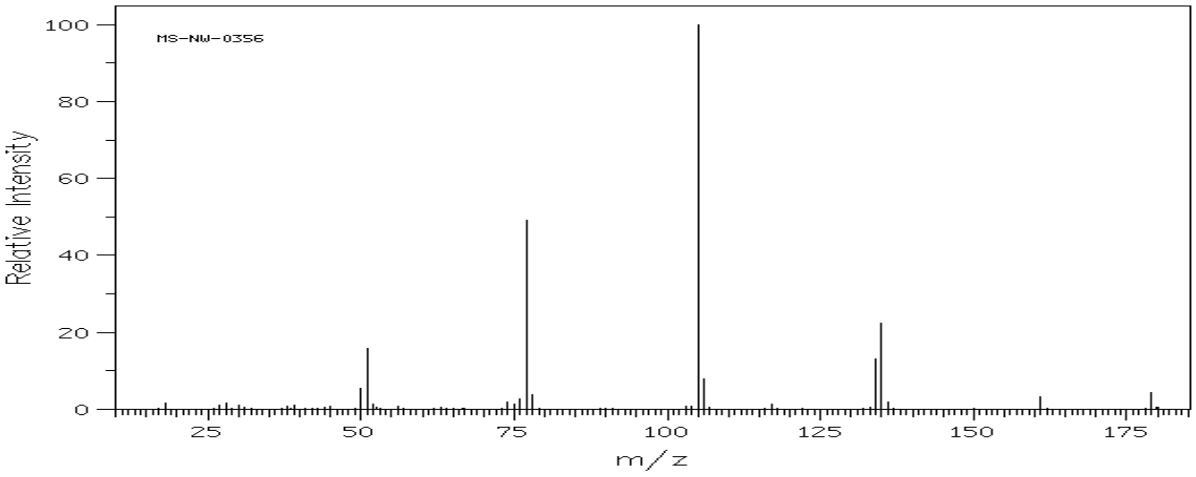
Put substrate and product onto SiO_2 plate (as a solution in MeOH), then place the plate into developing chamber with chloroform/methanol (8:2). Remove the plate and allow the solvent to evaporate. The spot of hippuric acid is visible in the UV light. Mark the spot in pencil. Then, using forceps, dip the plate into the mixture of SiO_2/I_2.

SPECTRA

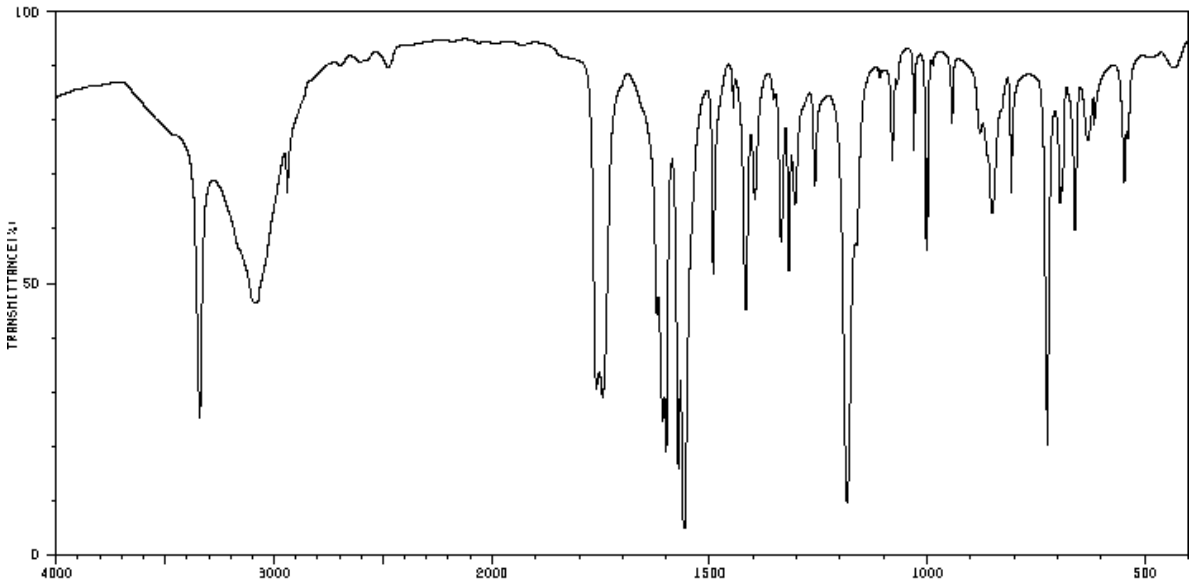
MS, FT-IR and NMR spectra of benzoyl chloride in chapter 15. Flavone.

MS, FT-IR and NMR spectra of glycine in chapter 23. *N*-Phtaloylglycine.

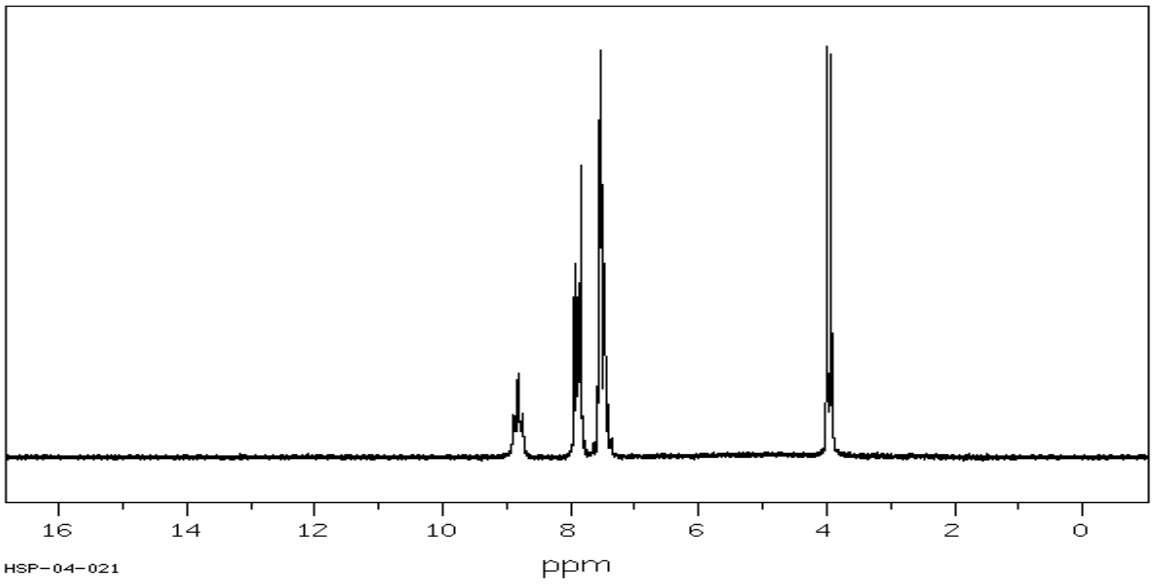
a) EI-MS spectrum of hippuric acid.



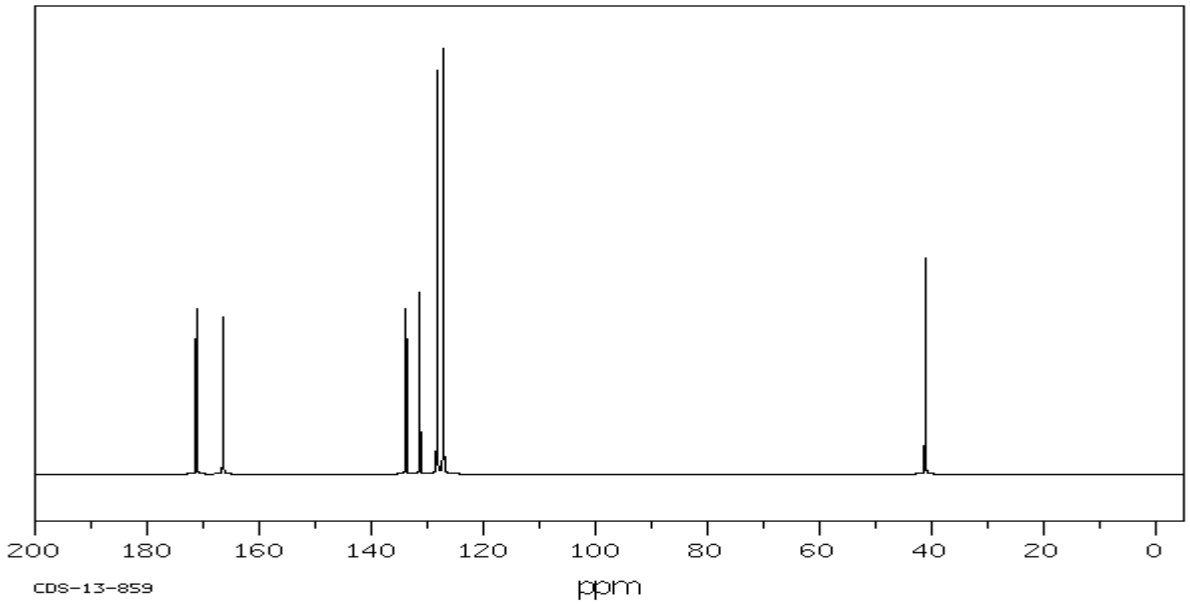
b) IR spectra of hippuric acid (KBr).



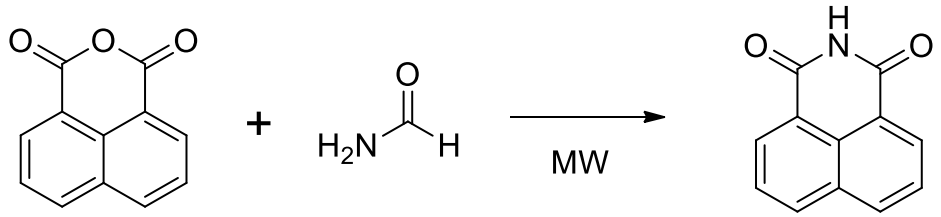
c) ^{1}H-NMR spectrum of hippuric acid in DMSO-$_{d6}$ (90Hz).



d) ^{13}C NMR spectrum of hippuric acid in DMSO-*d*$_6$.



25. 1,8-NAPHTHALIMIDE



Reagents:		**Instrumentation and glassware:**
1,8-naphthalic anhydride	0.2 g	round-bottom flask 50 mL
formamide	3 mL	stirring bar
		filtering flask with Büchner funnel

Freshly ground 1,8-naphthalic anhydride (0.2 g) place in a 50 ml round-bottom flask, and add formamide (3 mL). The reaction mixture is subjected to microwave radiation (100 ^{o}C or 700 W) for 5–8 minutes. After cooling, add carefully water (10 mL), and filter off the crystalline imide (lit. m.p. = 299–300 ^{o}C).

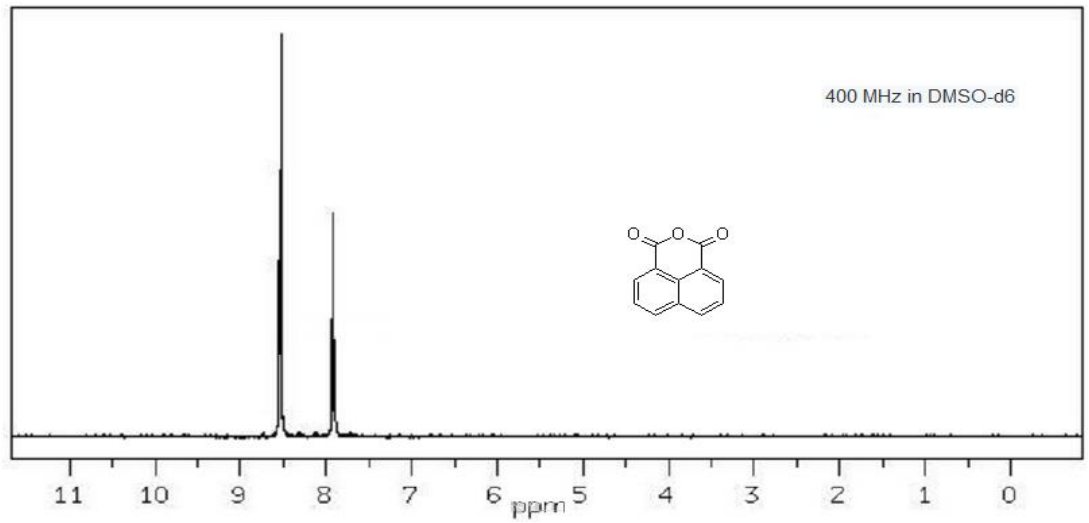
Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate).

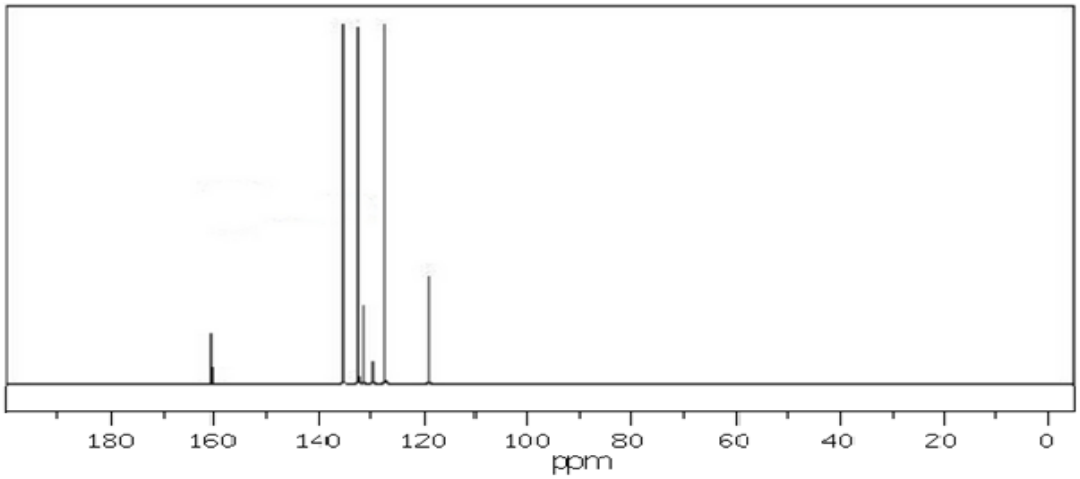
Develop with chloroform/methanol (15:1). Remove the plate and allow the solvent to evaporate and inspect under UV light. Mark the spots with pencil. Then, using forceps, dip the plate into closed jar containing SiO_2 saturated with I_2.

SPECTRA

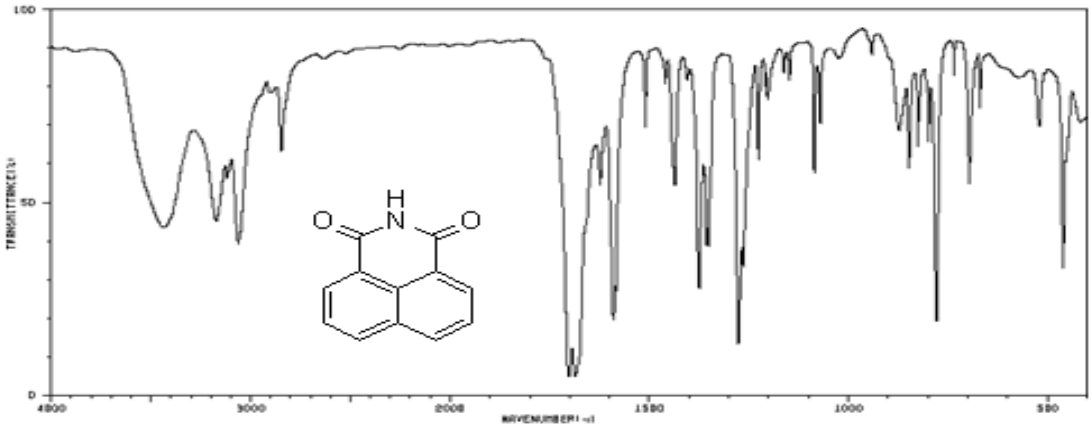
a) ^{1}H NMR spectrum of 1,8-naphthalic anhydride in DMSO-d_6.



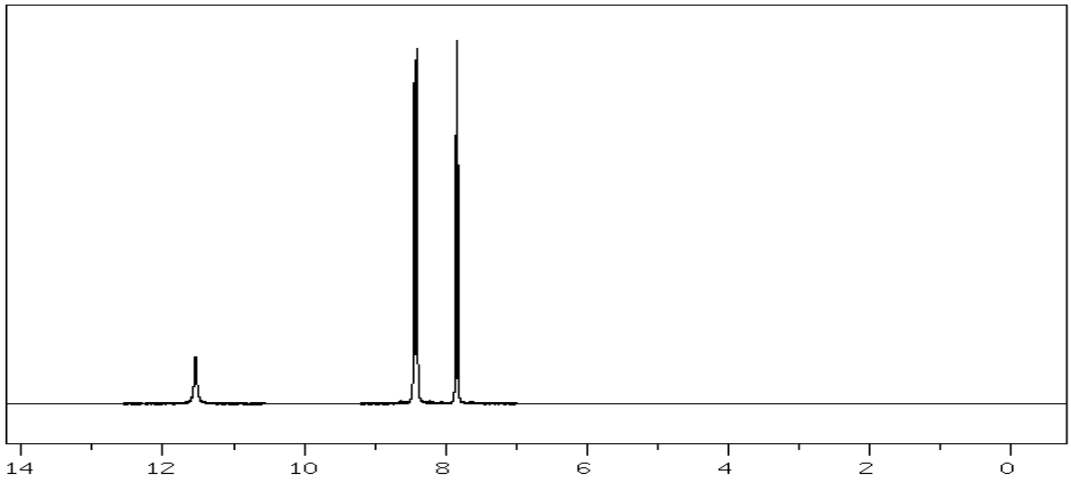
b) ^{13}C NMR spectrum of 1,8-naphthalic anhydride in in DMSO-d_6.



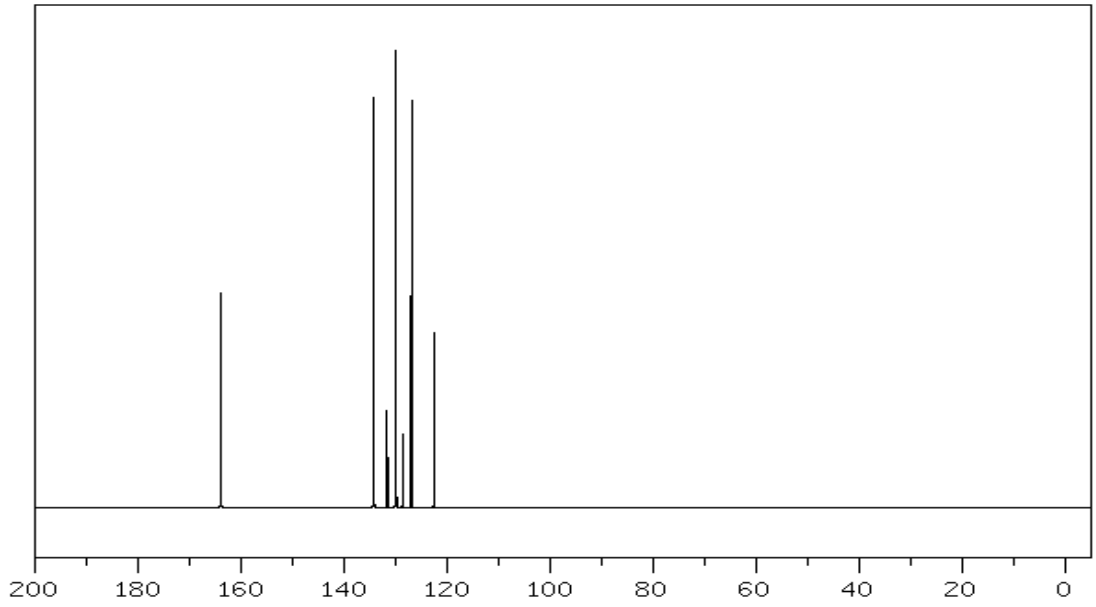
c) FT-IR spectrum of 1,8-naphthalimide in KBr disc.



d) ^{1}H NMR spectrum of 1,8-naphthalimide in DMSO-d_6.



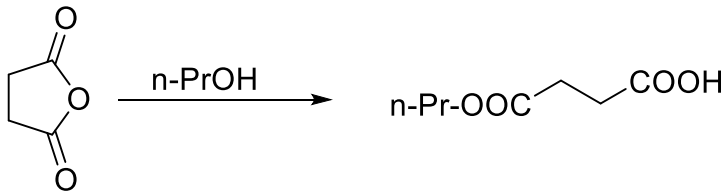
e) ^{13}C NMR spectrum of 1,8-naphthalimide in chloroform-*d*.



26. *N*,*N*-DIETHYL-SUCCINAMIC ACID PROPYL ESTER

(3-step synthesis)

STEP 1 4-OXO-4-PROPOXYBUTANOIC ACID



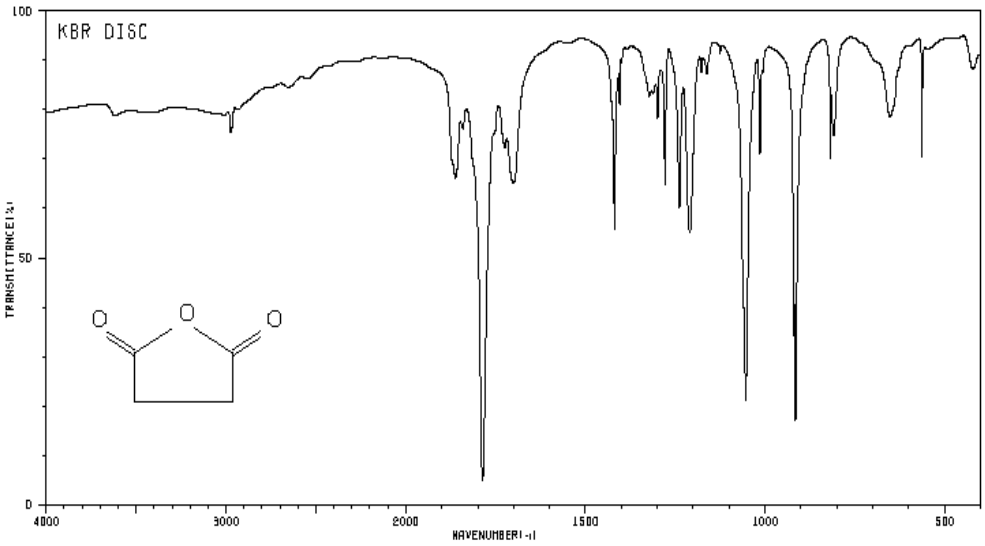
Reagents:		**Instrumentation and glassware:**
succinic anhydride	2 g	round-bottom flask 25 mL
n-propanol	3 mL	magnetic stirrer with heating magnetic dipole

Place a mixture of 2 g of succinic anhydride and 3 mL of *n*-propanol in a 25 mL round-bottom flask equipped with a reflux condenser, and reflux it for 30 minutes. After cooling, remove the excess *n*-propanol by distillation under reduced pressure (use rotary evaporator). The product that remains in the flask is pure enough for the direct use in the next reaction.

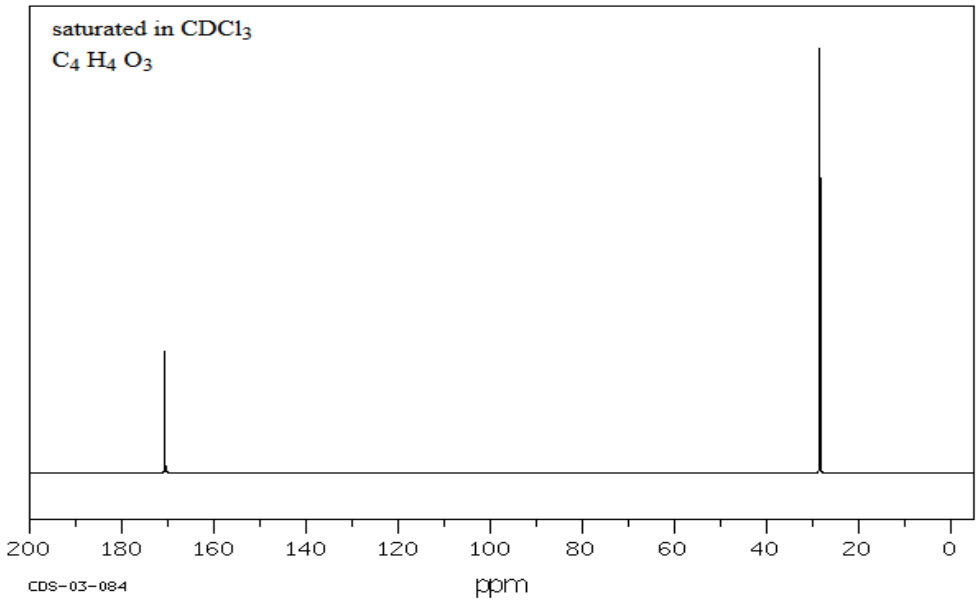
Yield: 3.2 g (99%), colorless liquid.

SPECTRA

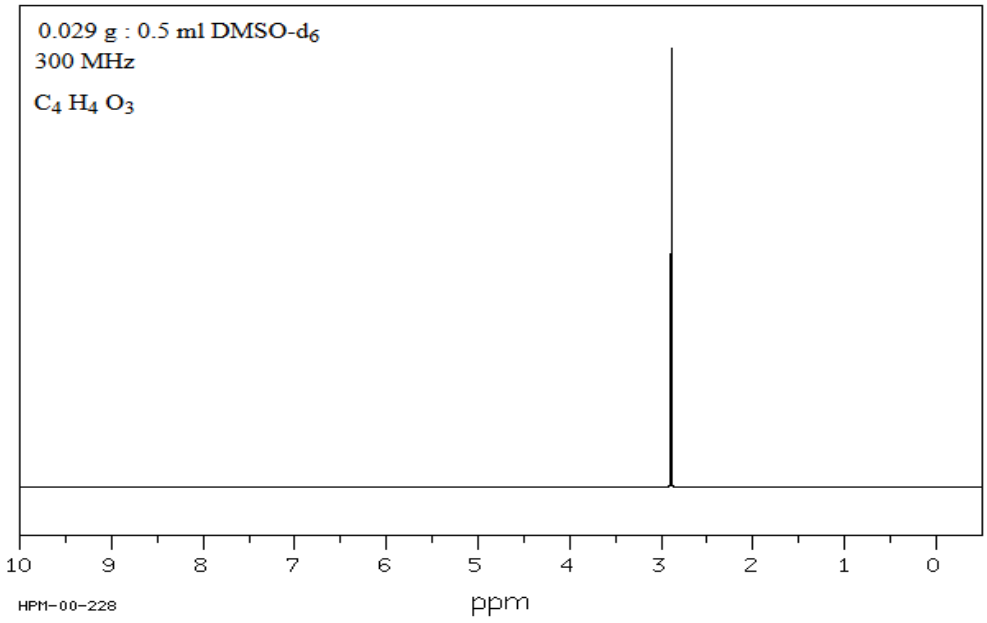
a) FT-IR spectrum of succinic acid in KBr disc.



b) ^{13}C NMR spectrum of succinic acid in chloroform-*d*.



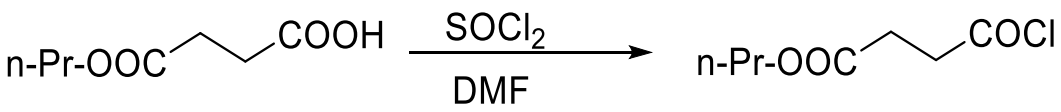
c) ^{1}H NMR spectrum of succinic acid in DMSO-d_6.



d) **FT-IR spectrum** of 4-oxo-4-propoxybutanoic acid (film): 3400–2400, 1720, 1710, 1480, 1400, 1085 and 1030 cm^{-1}.

e) **^{1}H NMR spectrum** of 4-oxo-4-propoxybutanoic acid: 0.9 (t, 3H), 1.6 (m, 2H), 2.6 (s, 4H), 4.0 (t, 2H), 11.0 (s, 1H) ppm.

STEP 2 4-OXO-4-PROPOXYBUTANOIC ACID CHLORIDE



Reagents:		**Instrumentation and glassware:**
4-oxo-4-propoxybutanoic acid	3.2 g	round-bottom flask 25 mL
$SOCl_2$	2.9 mL	condenser
DMF	1 drop	magnetic stirrer with heating magnetic dipole

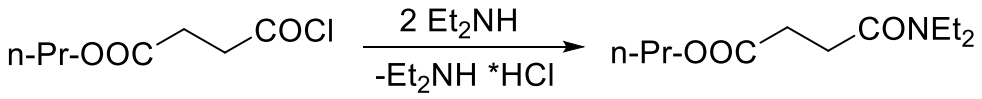
Due to the irritating vapors of $SOCl_2$ and products of its decomposition, all operations with this reagent should be carried out under the fume hood!

Add 3.2 g of 4-oxo-4-propoxybutanoic acid to 2.9 mL of $SOCl_2$ with a drop of *N*,*N*-dimethylformamide in a 25 ml flask equipped with a reflux condenser. Stir the reaction mixture at room temperature for 20 min.

The evolving hydrogen chloride must be neutralized or directed to fuming hood.

Next, heat the mixture under reflux in an oil bath for 15 min. Evaporate the excess of $SOCl_2$ (rotary evaporator). Remove the residues of $SOCl_2$ from the reaction mixture by adding 5 ml of *n*-hexane and subsequent evaporation. Use the crude acid chloride obtained in the next step of synthesis without purification.

STEP 3 PROPYL 4-(DIETHYLAMINO)-4-OXOBUTANOATE.



Reagents:

4-oxo-4-propoxybutanoic acid chloride	3.56 g
diethylamine	3 mL
CH_2Cl_2	10 mL
3M HCl	10 mL
5% $NaHCO_3$	10 mL
Anh. Na_2SO_4	

Instrumentation and glassware:

Three-necked round-bottom flask 100 mL
condenser
dropping funnel
magnetic stirrer
glass stopper
separatory funnel

Notes:

Diethylamine vapors are irritating. All operations with diethylamine should be done under the fume hood.

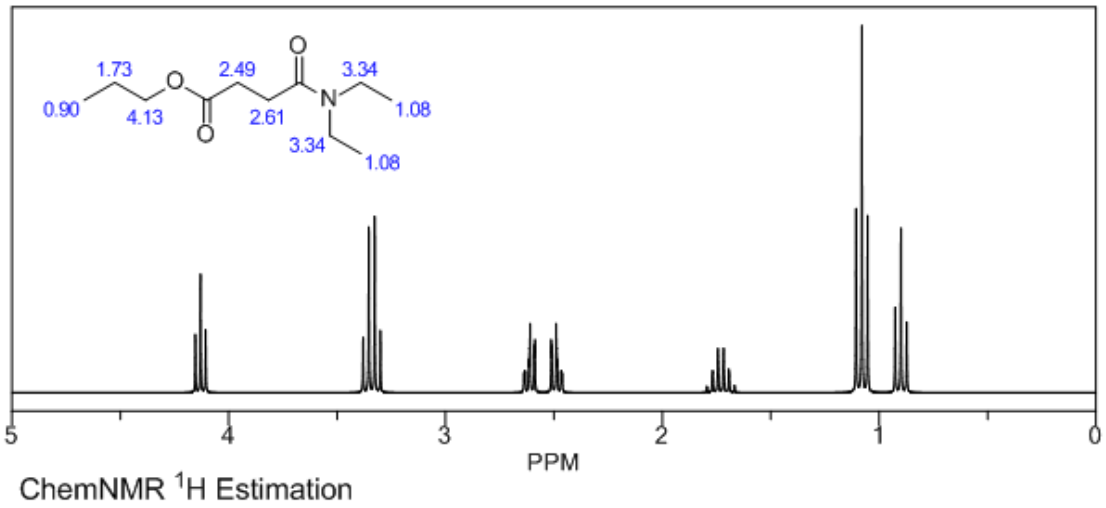
Place 3 mL of diethylamine in 10 mL of CH_2Cl_2 in 100 mL three-necked round-bottom flask, supplied with a reflux condenser, dropping funnel, glass stopper and magnetic stirrer. After starting the magnetic stirrer, add carefully (dropwise) the acid chloride solution (exothermic reaction). Continue stirring for 15 min after the addition of the acid chloride, and then add 20 mL of water to dissolve the precipitated diethylamine hydrochloride.

Separate the aqueous and CH_2Cl_2 layers using the separatory funnel. Wash the CH_2Cl_2 solution twice with 10 mL of 3M HCl and 10 mL of 5% $NaHCO_3$, then dry over anh. Na_2SO_4 or $MgSO_4$. Remove CH_2Cl_2 by evaporation. The crude product is obtained in a yield of 3.5 g (71%). The product can be purified by kugel-Rohr distillation (bulb to bulb distillation) under reduced pressure (bp 124.5–125 °C / 2 mm Hg).

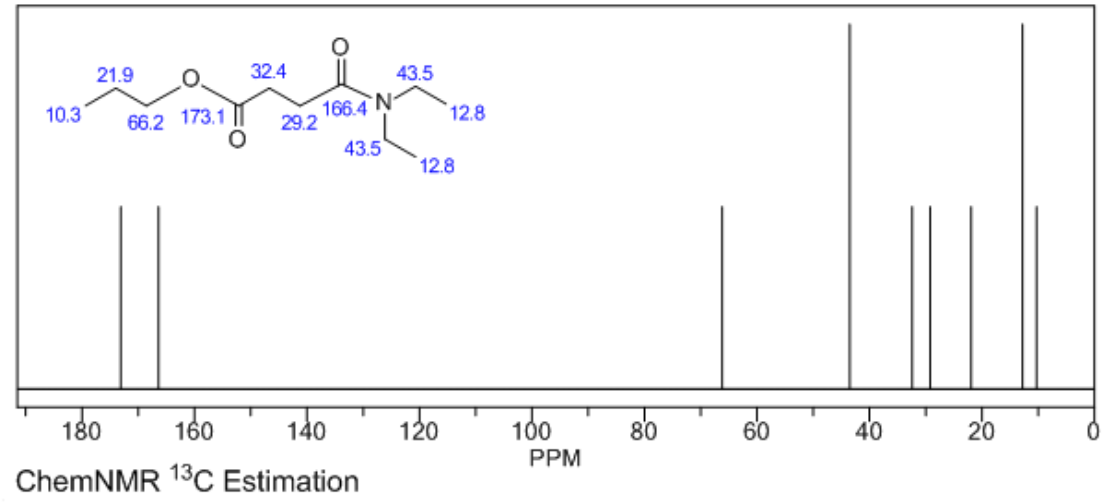
SPECTRA

a) **FT-IR** of propyl-4-(diethylamino)-4-oxobutanoate: 3000–2850, 1720, 1640, 1470, 1180, 1140 cm^{-1}.

b) **^{1}H NMR** of propyl-4-(diethylamino)-4-oxobutanoate: 0.9–1.6 (m, 11H), 2.6 (s, 4H), 3.3 (q, 4H), 3.95 (t, 2H) ppm.



c) **^{13}C NMR** of propyl-4-(diethylamino)-4-oxobutanoate.



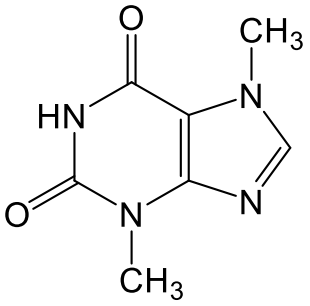
References

Caudle R., Siegel G., Wood W. F.: Preparation of Propyl N,N-Diethylsuccinimate: An Insect Repellent. *J. Chem. Ed*. 59, 1069 (1982).

Svirbely W. J., Eareckson W. M., Matsuda K., Pickard H. B., Solet J. S., Tuemmler W. B.: Physical Properties of Some Organic Insect Repellents. , *J. Am. Chem. Soc.* 71, 507 (1949).

Gawroński J., Gawrońska K., Kacprzak K., Kwit M.: *Współczesna synteza organiczna. Wybór eksperymentów*, Wydawnictwo Naukowe PWN, 2012.

27. THEOBROMINE (extraction)

COCOA POWDER 

Reagents:		**Instrumentation and glassware:**
Cocoa powder	10 g	Heating mantle
Magnesium oxide (MgO)	3 g	Round flask 250 mL
Methanol	10 mL	Measuring cylinder
Methylene chloride	350 mL	Round flask 100 mL
Diethyl ether	65 mL	Cooler
Iodine (I_2)	1 g	Glass rod
Potassium iodide (KI)	2 g	filtration kit with Büchner funnel
Ethanol	100 mL	beaker 100 mL

METHOD A

In a round bottom flask (250 mL) prepare the mixture of cocoa powder (10 g) and methanol (10 mL) then add the suspended MgO (3g) in water (10 mL). The mixture is stirred with a glass rod and heated in heating mantle to dryness. It takes approximately 1 hour. To the dry substance received add 170 mL of methylene chloride and heat under reflux for 30 min. Then filter the contents through "Celite cake" on a Büchner funnel. Crush the brown solid and once more put it into a round bottom flask, add 170 mL of methylene chloride. Heat the mixture under reflux for additional 30 min and once more filter on the Büchner funnel.

Combine the organic fractions and dry the solution over anh. sodium sulphate, then filtrate through the funnel with cotton plug to remove drying agent. Transfer the combined fractions into a clean and dry round-bottom flask (100 mL) and concentrate the solution to 10 mL. Add 45 mL of diethyl ether and leave to crystallization to obtain micro-crystals then wash them on a Büchner funnel 5 times with 10 mL of diethyl ether. The yield ca. 0.15 g of theobromine, m.p. 351 ^{o}C.

Thin layer chromatography (TLC): on SiO_2, the spots of product and standard theobromine have to be very intensive (!) - check under UV light before developing the plate in the mobile phase: chloroform-hexane (9:0.5). Remove the plate and allow the solvent to evaporate. The spot of theobromine is visible in the UV light. Mark the spot in pencil. Then dip the plate into the reagent

prepared in advance: I_2 (1g), KI (2 g) in EtOH (100 mL). After drying, using forceps dip your plate into the mixture of 25% HCl and ethanol (1:1). The spot of theobromine turns gray-bluish and impurities of caffeine turn brownish-reddish.

METHOD B

Reagents:		**Instrumentation and glassware:**
Cocoa powder	10 g	Soxhlet apparatus
Magnesium oxide (MgO)	3 g	Heating mantle
Methanol	10 mL	Round flask 250 mL
Methylene chloride	350 mL	Measuring cylinder
Diethyl ether	65 mL	Round flask 100 mL
Iodine (I2)	1 g	Cooler
Potassium iodide (KI)	2 g	filtration kit with Büchner funnel
Ethanol	100 mL	beaker 100 mL

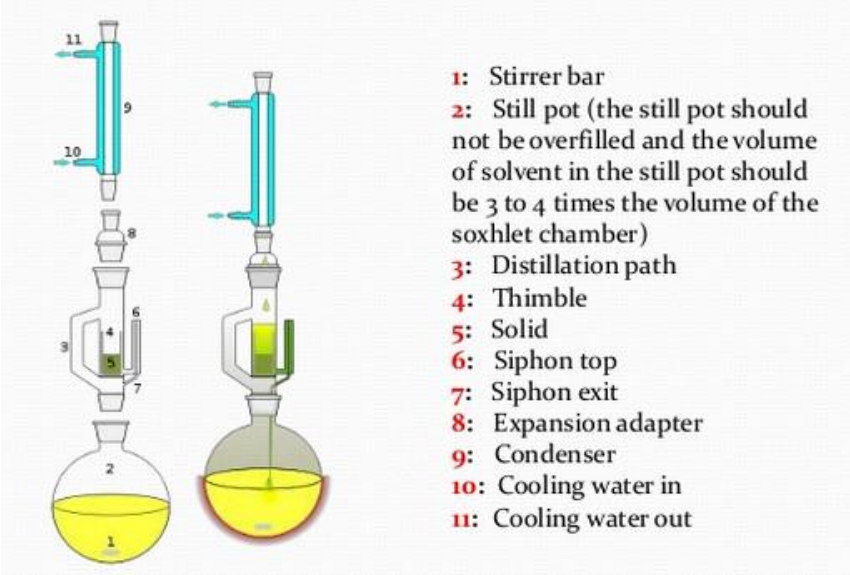


Figure 5. Soxhlet apparatus. https://www.slideshare.net/AbarnaAbi1/soxhlet-apparatus

In a beaker, mix magnesium oxide (3 g) with 10 ml of water. Add cocoa (10g) to this slurry and mix again so that there are no lumps. Then add 4.5 g of diatomaceous earth (Celite) and mix until a loose consistency. Transfer the resulting mixture to a thimble (cover the top of the thimble with cotton) and insert into the Soxhlet apparatus - Fig. 5.

Be sure to put the boiling stones in the distillation flask.

Into the system with the thimble, gently add 100 mL of methylene chloride from the top of the Soxhlet so that the thimble with a mixture of cocoa and Celite is first washed.

Wait for the solvent to overflow through the siphon into the flask and repeat the process with another 100 mL of methylene chloride. When the distillation flask is half full close the system with condenser and start heating. Heat to reflux for 1 hour.

After cooling, add a drying agent (anhydrous Na_2SO_4) to the flask and, after drying, filter the solution directly into the tared round-bottomed flask. Perform a purity analysis (TLC) of the resulting crude product, then evaporate the solvent on a vacuum evaporator and weigh theobromine. Recrystallize the obtained compound from the mixture of methylene chloride-diethyl ether mixture (5:20, v/ v). Transfer the solution with the Pasteur pipette into the vial. Filter off the resulting microcrystalline precipitate on a small Büchner funnel and wash with 5 mL diethyl ether. Weigh the obtained theobromine and calculate its content in cocoa (m.p. 351^{o}C). Compare the obtained mass and purity (TLC) of the product obtained by method A and method B.

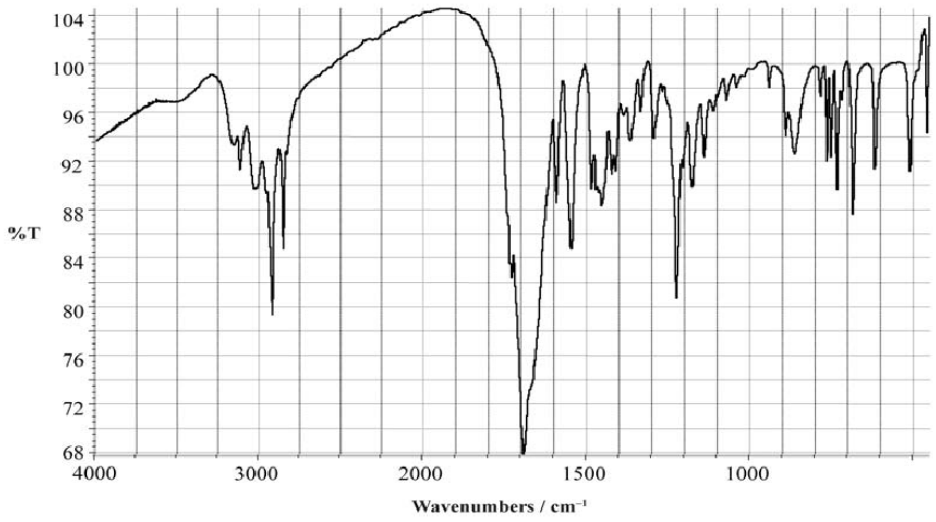
Thin layer chromatography (TLC): on SiO_2, the spots of product and standard theobromine have to be very intensive (!) - check under UV light before developing the plate in the mobile phase: chloroform-hexane (9:0.5). Remove the plate and allow the solvent to evaporate.

The spot of theobromine is visible in the UV light. Mark the spot in pencil.

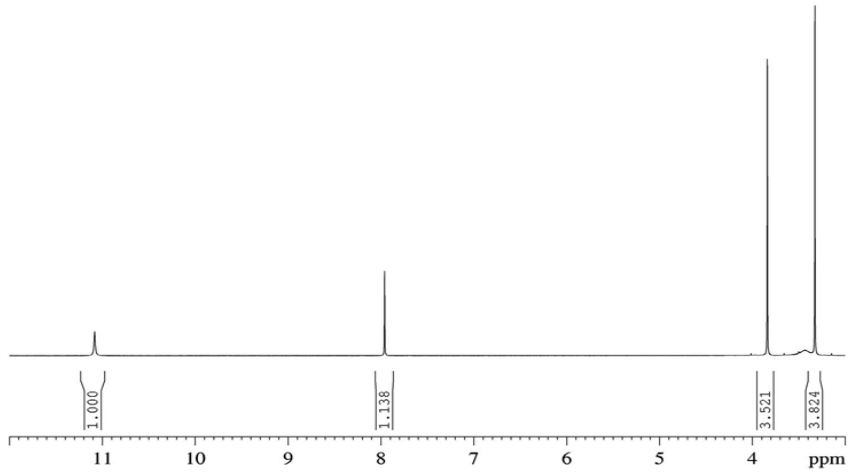
Then dip the plate into the reagent prepared in advance: I_2 (1g), KI (2 g) in EtOH (100 mL). After drying, using forceps dip your plate into the mixture of 25% HCl and ethanol (1:1). The spot of theobromine turns gray-bluish and impurities of caffeine turn brownish-reddish.

SPECTRA

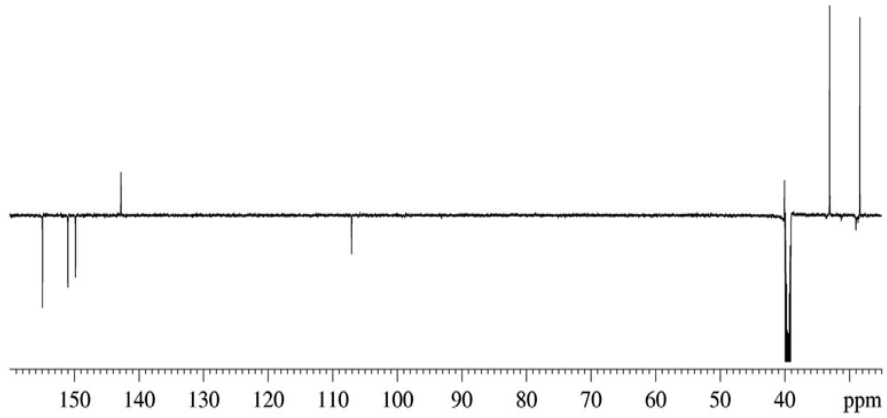
a) FT IR spectrum of theobromine in KBr tablet.



b) ^{1}H NMR spectrum of theobromine in DMSO-d_6 (400 MHz).



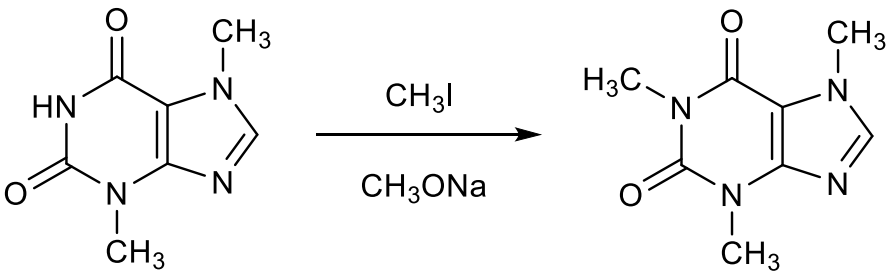
c) APT ^{13}C NMR spectrum of theobromine in DMSO-d_6 (400 MHz).



References

https://www.slideshare.net/AbarnaAbi1/soxhlet-apparatus

28. CAFFEINE



theobromine caffeine

Reagents:		**Instrumentation and glassware:**
Theobromine	0.2 g	Magnetic stirrer
Sodium	0.05 g	Measuring cylinder
methylene iodide	2.4 mL	Round bottom flask 25 mL with stopper (x2)
anh. methanol	12 mL	Syringe 1 mL
methylene chloride		Separatory funnel 50 mL
anh. sodium sulfate		Conical flask 50 mL

Notes!

Work under hood. Gloves, goggles and a face mask are mandatory. Anhydrous condition.

A) Prepare the sodium methoxide solution in a flask protected against moisture.

To a 25 mL round-bottomed flask containing 6 mL of anhydrous methanol, gradually add (in 3-4 portions) 0.05 g of sodium. Another portion of sodium can be introduced after reconstitution of the previous portion. When the dissolution rate of sodium is significantly reduced, carefully add an additional amount (approx. 2 mL) of anhydrous methanol to the flask.

If necessary, cool the flask in a water-ice bath.

B) In a 25 mL round-bottom flask (equipped with a magnetic bar), suspend 0.2 g of theobromine in 6 mL of anh. methanol (note that theobromine is not dissolved in methanol). Add freshly prepared sodium methoxide (obtained by reacting 0.05 g of sodium with 6 mL of anh. methanol – look **point A**) and stir gently for ten minutes by using a magnetic stirrer. When the solution turns translusit and yellow it means that theobromine has dissolved completely.

Then add 2.4 mL of CH_3I with a syringe (the size of 1 mL). Stopper the flask. Start the reaction and use magnetic stirrer. Monitor the reaction by TLC (use an eluent system CH_2Cl_2 97:3) at 30, 60 and 90 minutes comparing with theobromine.

After completion of the reaction, evaporate the solvent using a rotavapor. Then add 15 mL of water and shake vigorously and extract product with CH_2Cl_2 (3x15 mL). Combine the organic layers and dry above sodium sulphate, then filter and evaporate the solvent with caffeine in a rotavapor. The crude caffeine is obtained in the form of a brown solid (the yield 90%). To purify caffeine recrystalize it from acetone or an acetone-petroleum ether solvent system.

By determining the melting point and comparing it with the authentic standard (m.p. 234–236°C), identify the product as caffeine.

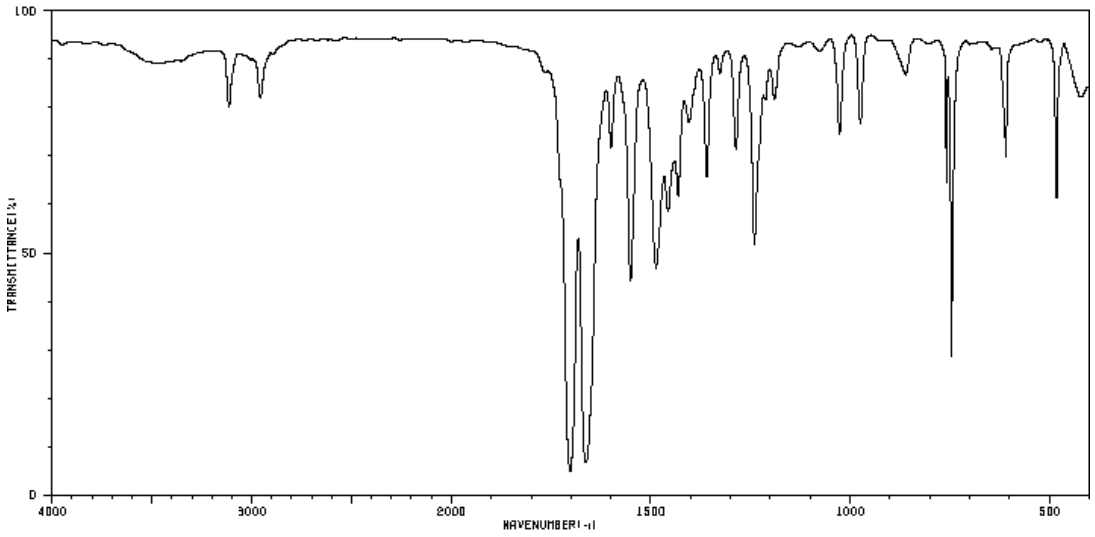
Thin layer chromatography (TLC): on SiO_2, the spots of the product and standard caffeine have to be very intensive (!) - check under UV lamp before developing the plate in the eluent: CH_2Cl_2: MeOH (97:3) or chloroform.

Remove the plate and allow the solvent to evaporate. The spot of caffeine, like theobromine, is visible in the UV light. Mark the spots in pencil and calculate the retention factor (Rf).

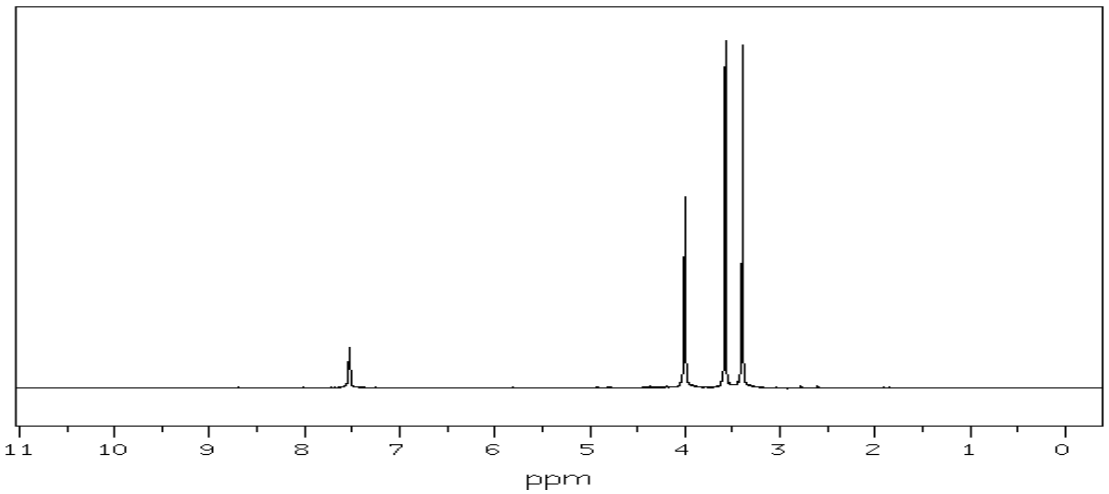
Then dip the plate into the prepared reagent: I_2 (1g), KI (2 g) in EtOH (100 mL). After drying, using forceps dip your plate into the mixture of 25% HCl and ethanol (1:1). The spot of theobromine turns gray-bluish and caffeine turn brownish-reddish.

SPECTRA

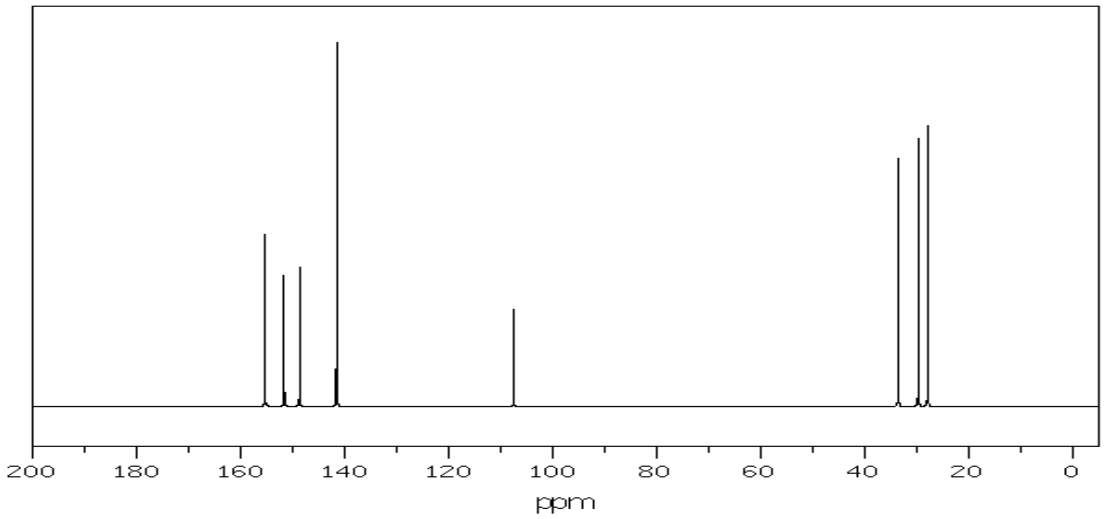
a) FTIR spectrum of caffeine in KBr disc.



b) ^{1}H NMR spectrum of caffeine in $CDCl_3$ (90 MHz).



c) ^{13}C NMR spectrum of caffeine in $CDCl_3$ (90 MHz).



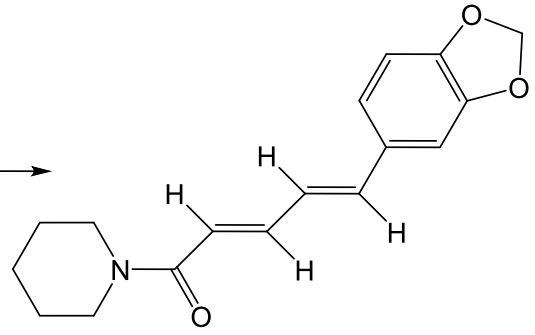
References

González-Calderón D., González-González C. A., Fuentes-Benítes A., González-Romero C.: Synthesis of caffeine from theobromine: bringing back an old experiment in a new setting. *Educ. quím.*, *26* (2015) 9-12.

Clarke R. J.: The Flavour of Coffee. *Dev. Food Science*, *3B*, 1986, 1-47.

http://www.coffeeresearch.org/science/sourmain.htm

29. PIPERINE

BLACK PEPPER 

Reagents:

black pepper 20 g
chloroform 100 mL
10% KOH in 50% EtOH
toluene
cyclohexane

Instrumentation and glassware:

Soxhlet apparatus with condenser
conical flask 100 mL
crystallizing dish
heating mantle
round bottom flask 50 mL
filtering flask with Büchner funnel
beaker 100 mL

Place powdered black pepper (20 g) in the thimble of a Soxhlet apparatus **(Fig. 5**., Chapter 27) and extract with chloroform for 2 h to obtain the piperine solution. At the end of this operation, the extract obtained is colorless. All of the solvent is removed in vacuo and a brown oil remains.

The extract contains all lipophilic constituents of low polarity. In the concentrated extract, triglycerides present are cleaved by saponification with aqueous ethanolic KOH solution, whereas crude piperine crystallizes on standing in the cold.

Add 20 mL of a 10% KOH solution in 50% aqueous ethanol. Stir the mixture for 10 min and filter on the Büchner funnel. Allow to stand the filtrate overnight in a refrigerator at 4 °C. Filter the obtain crystals of crude piperine on the Büchner funnel and wash with 2 mL of cold water to remove the adhering base. Air-dry the crystals and recrystallize from cyclohexane/toluene (4:1, v/v). Use 10 mL of this solvent for each 200 mg of crude piperine (recovery ca. 60%). Piperine crystallizes on standing in a beaker as shiny, pale yellow crystals. Filter the crystals and wash them with a few mL of cyclohexane, m.p. 130-131 °C. Yield: 200-500 mg depending on the pepper.

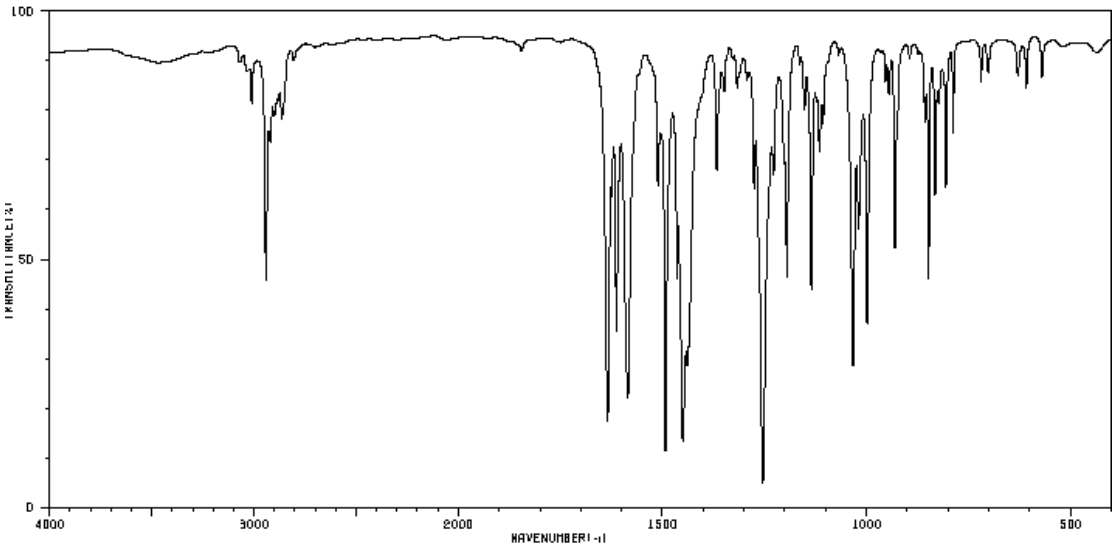
Thin layer chromatography (TLC):

Apply the substrate and product onto SiO_2 plate with capillary, then place the plate vertically into developing tank (small beaker, covered with glass plate). Develop with toluene/ethyl acetate (1:1). Remove the plate and allow the solvent to evaporate. The spot of piperine is visible under the UV

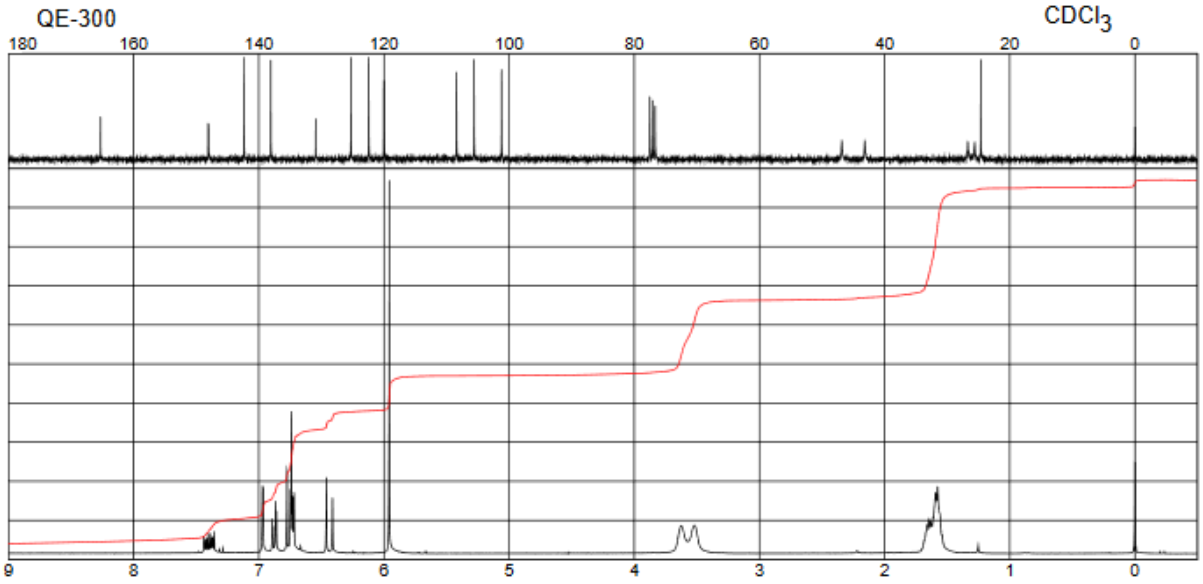
light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2. Besides the desired main compound (Rf = 0.53), a second stereoisomer (Rf = 0.26) of higher polarity is present.

SPECTRA

a) FT IR spectrum of piperine in KBr tablet.

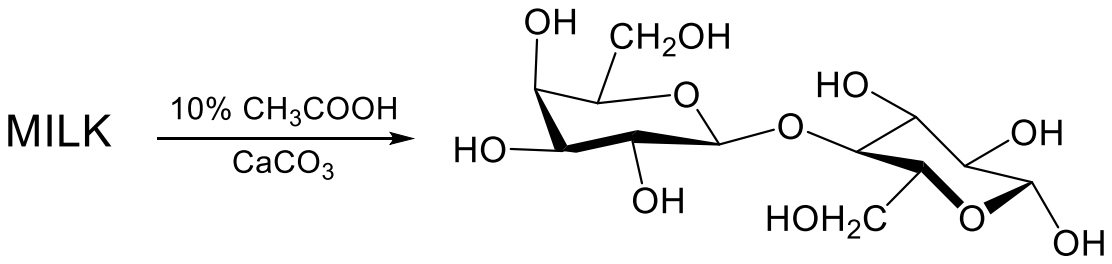


b) ^{1}H NMR and ^{13}C NMR spectra of piperine in $CDCl_3$ (400 MHz).



https://www.sigmaaldrich.com/catalog/

30. LACTOSE



Reagents:

Powdered skimmed milk	30 g
Acetic acid 10%	18 mL
Calcium carbonate	2.4 g
Ethanol	150 mL
Activated carbon	

Instrumentation and glassware:

magnetic stirrer
beaker 300 mL
measuring cylinder
filtering system with Büchner funnel
round bottom flask 250 mL

Insert into the beaker 30 g f milk powder and suspend it in 60 mL of warm water (it is possible to use 200 mL skimmed milk (0% or 0.5%)) and stir the mixture at 40-50 ^{o}C for 15 min. Then add slowly 10 mL of 20 % acetic acid, stirring the mixture. The coagulation of casein starts. Remove the casein by decantation and pass the rest through the cotton cloth. Weigh it and calculate the yield.

Pour the resulting translucent solution into a beaker and bring to the boil. Carefully mix the hot solution with calcium carbonate (2.4 g) for about 10 minutes. (Attention! The solution foams quickly! Immerse the beaker in the crystallizing vessel!) To the warm mixture add a pinch of activated carbon and after mixing, filter the warm mixture on a Büchner funnel with Celite cake on the funnel. Then concentrate the clear solution to approximately 35 ml in a vacuum evaporator. Add 150 ml ethanol and an additional pinch of activated carbon. Once more filter the warm mixture through the "Celite cake" on the Büchner funnel. Concentrate the resulting filtrate on an evaporator to ca. 70 ml and allow the lactose to crystallize in a crystallization vessel with ice and water. Filter the resulting product on a Büchner funnel and rinse with cold ethanol.

The yield of lactose is ca. 3-5 g.

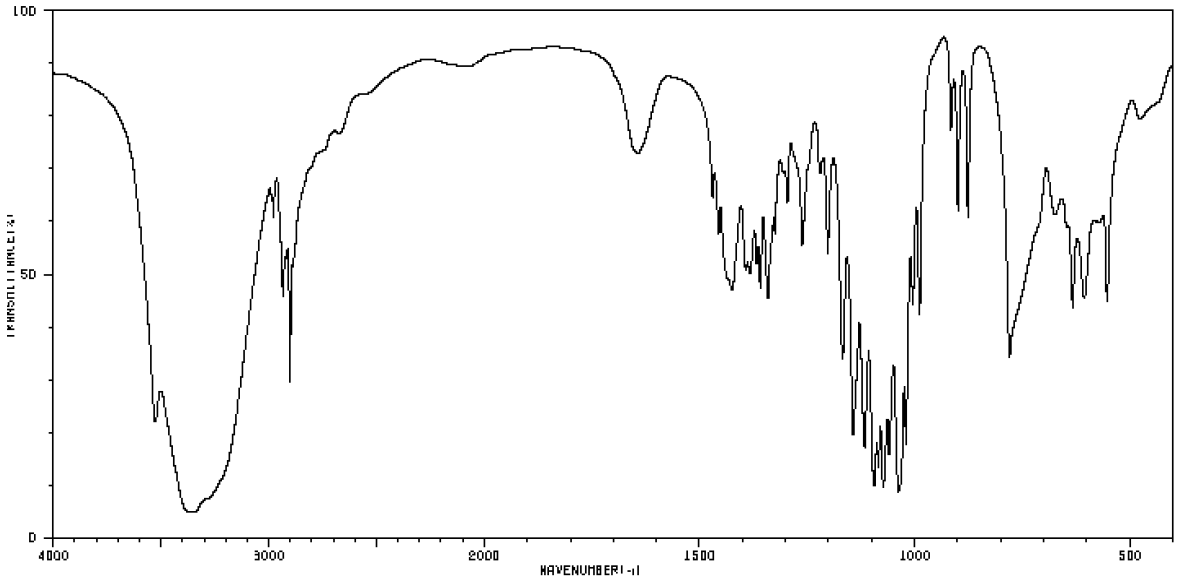
Thin layer chromatography (TLC): on SiO_2, toluene - anh. acetic acid - methanol (2:2:6).

After a few minutes the solvent will reach the upper line, remove the plate using forceps and allow the solvent to evaporate. After drying use a hot-plate and heat the TLC plate carefully and you will see spots developing on the plate. Be sure not to overheat the plate or it may crash!

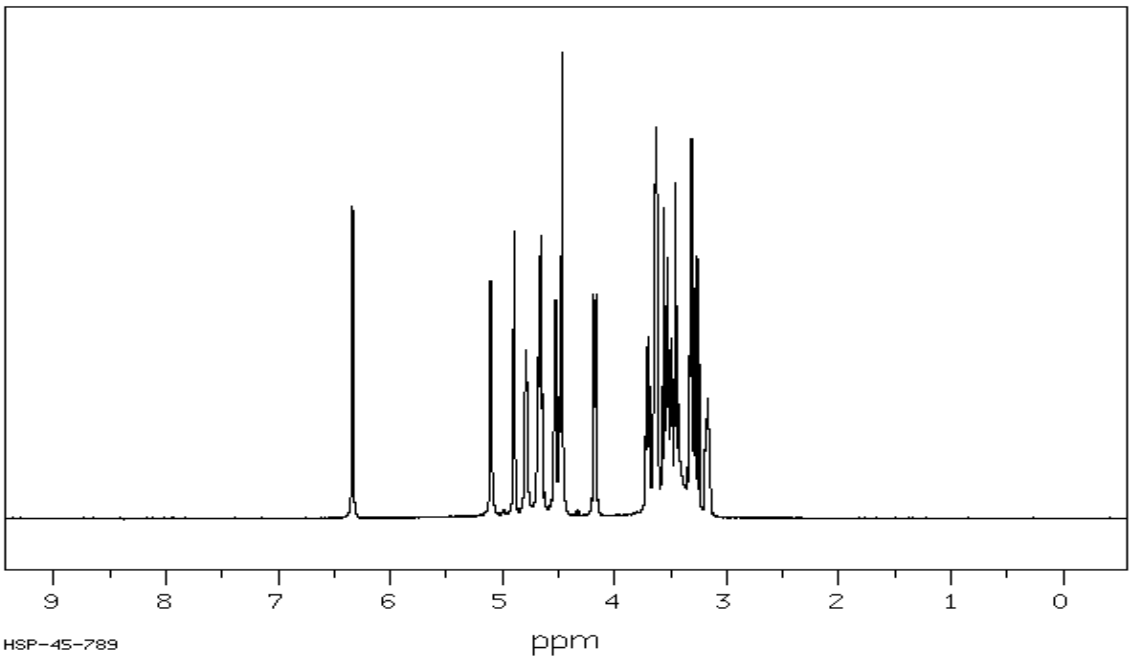
Wohlk's test: to the test tube add solution of the obtained product and boil it with KOH. If any disaccharide sugars are present a red colour appears. The colour will turn yellow-brownish in the presence of reducing sugars (glucose and fructose).

SPECTRA

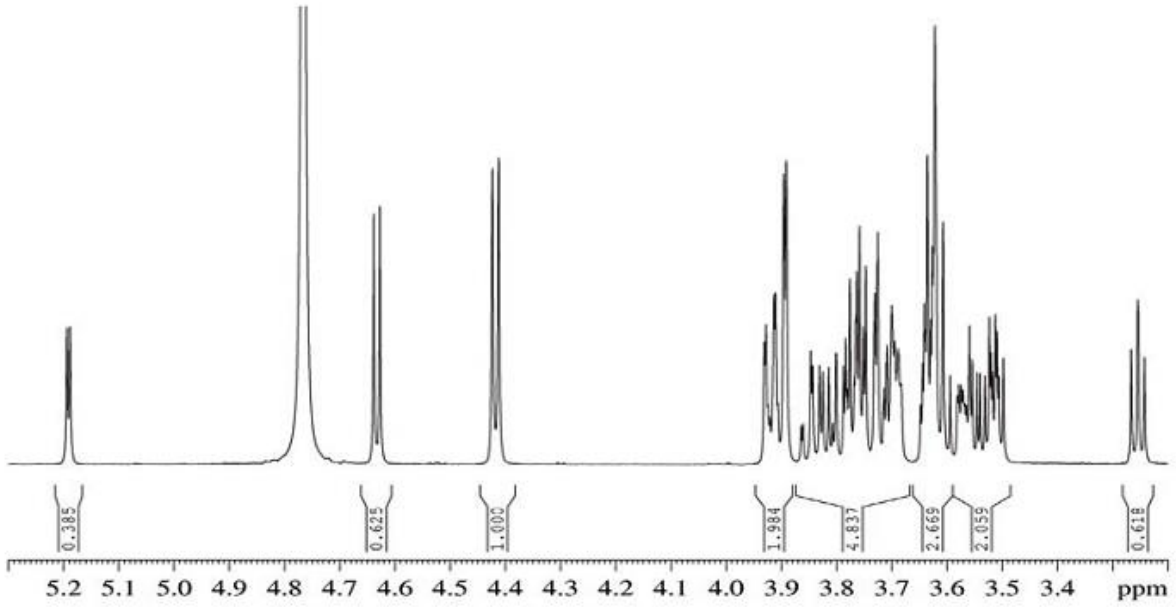
a) FTIR spectrum of lactose in KBr disc.



b) ^{1}H NMR spectrum of lactose in DMSO-d_6 (400 MHz).



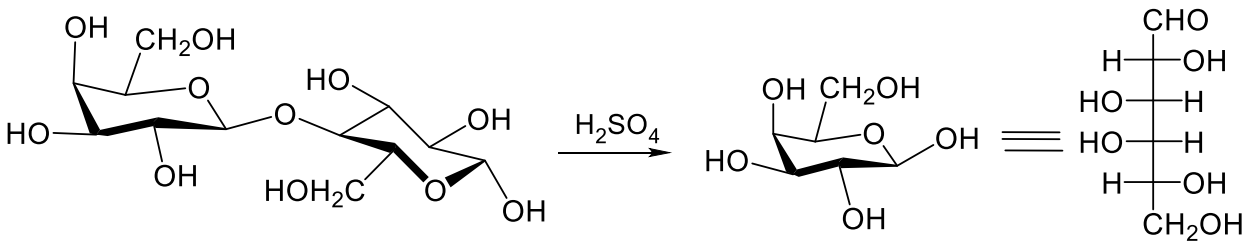
c) ^{1}H NMR spectrum of lactose in D_2O (700 MHz).



References

Lucas J. M., Kaneko J. J., Hirohara K., Kleiber M.: Separation of Milk Components, Chromatographic Isolation of Citric Acid and Lactose from Skim Milk. *J. Agric. Food Chem.*, *7* (1959) 638.
Wohlk, *Zeitschr. F. Anal. Ch*. (1904), 670. „Odczynnik na cukier mleczny i maltozę"
Chemik Polski, nr 21, 24 (11) maja 1905r (V), 408.

31. *D*-GALACTOSE



Reagents:		**Instrumentation and glassware:**
lactose	20 g (0.06 moles)	round-bottomed flask 250 mL
conc. sulfuric acid	0.6 mL	condenser
$Ba(OH)_2 \times 8H_2O$	3 g	filtering kit with Büchner funnel
anh acetic acid	25 mL	beaker 50 mL
methanol	5 mL	
diethyl ether	10 mL	

In a round-bottomed flask (250 mL) place 20 g of lactose, 40 mL water and 0.6 mL of conc. sulfuric acid. Adjust the Liebig cooler and heat under reflux for 2 hours.

To the hot mixture add a pinch of activated carbon and adjust to pH = 7 by adding barium hydroxide. After stirring and cooling down, filter the mixture on a Büchner funnel using 3-4 filter papers. Concentrate the obtained solution on an evaporator to 10 mL. Pour the obtained translucent filtrate into a beaker and acidify with 0.6 mL of anh. acetic acid and leave for crystallization of D-galactose in a crystallizer with ice and water. Filter the product obtained on a Büchner funnel and wash with acetic acid, then with methanol and next with diethyl ether. The yield 5 g (47%) of D-galactose m.p. 165 ^oC, $[\alpha]^{20} = +81.5^o$ (c=1, water)

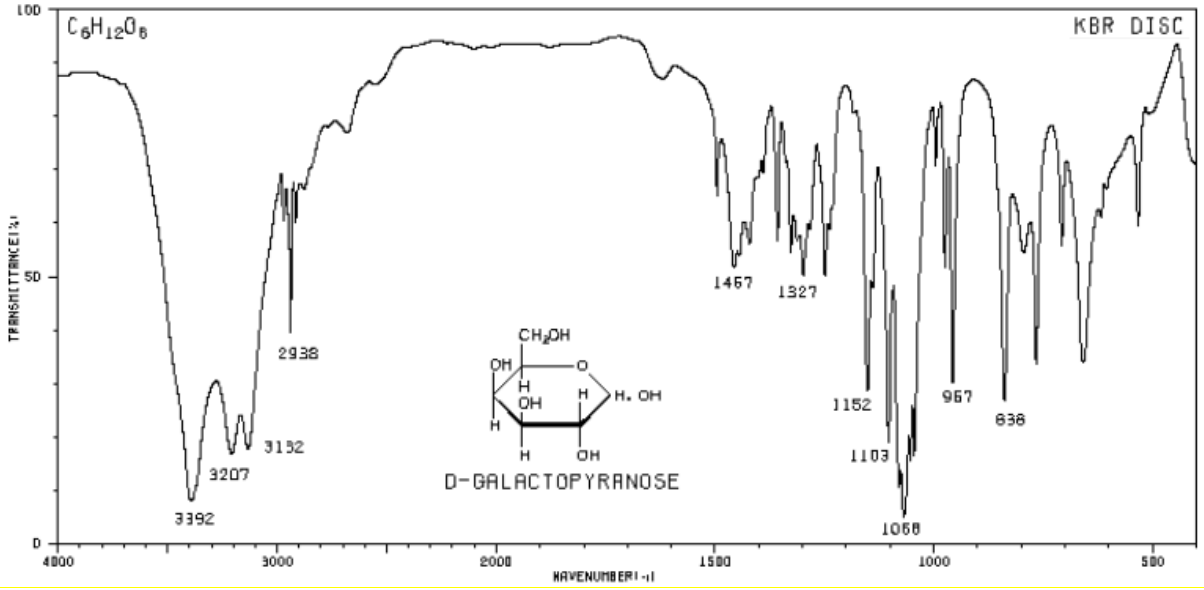
Thin layer chromatography (TLC):

on SiO_2: propanol – acetic acid-water (4:1:5). Remove the plate and allow the solvent to evaporate. After drying use a hot-plate and heat the TLC plate carefully and spots will develop on the plate.

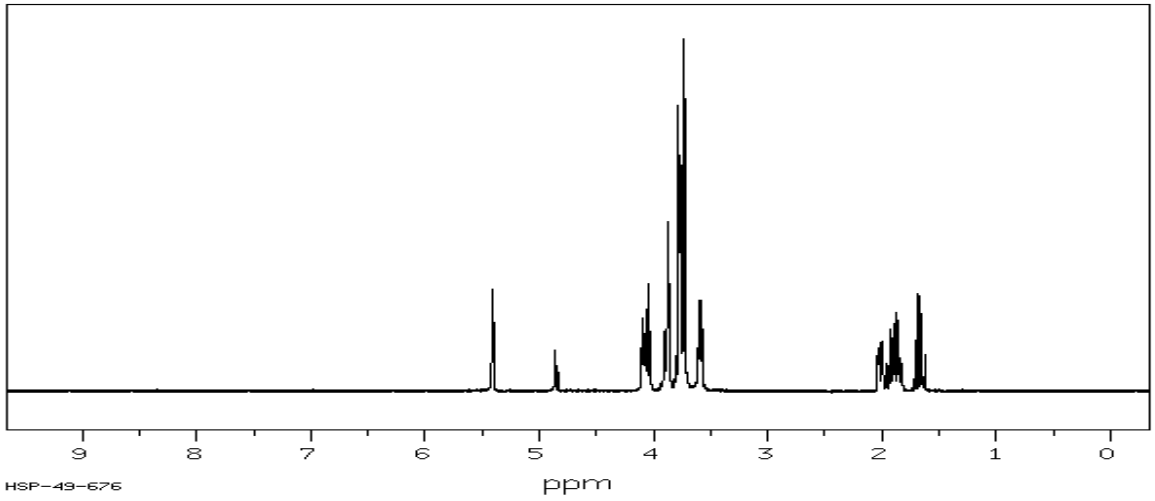
Barfoed's test: (in a tube) add a mixture of lactic acid (1 mL of 8,5%) and 1 g of $Cu(CH_3COO)_2$ in 19 mL of water to the test solution of product and boil. If any reducing sugars are present a red precipitate of Cu_2O is formed. The reaction will be negative in the presence of disaccharide sugars as they are weaker reducing agents.

SPECTRA

a) FTIR of *D*-galactose in KBr disc.



b) ^{1}H NMR spectrum of *D*-galactose in D_2O (400 MHz).

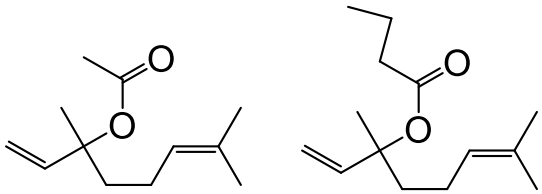


References

Lucas J. M., Kaneko J. J., Hirohara K., Kleiber M.: Separation of Milk Components, Chromatographic Isolation of Citric Acid and Lactose from Skim Milk. *J. Agric. Food Chem.*, 7 (1959) 638.
Wohlk, *Zeitschr. F. Anal. Ch.* **1904**, 670. „Odczynnik na cukier mleczny i maltozę”
Chemik Polski, nr 21, 24 (11) maja 1905r (V), 408.
http://www.chemistry.mcmaster.ca/~chem2ob3/nhw_temp/old_old_labmanual/expt5/2ob3exp5.html

32. ESTERS IN LAVENDER FLOWERS

LAWENDER FLOWERS ⟶



linalyl acetate linalyl butyrate

Reagents:

Part A

lavender flowers	15 g
dichloromethane	450 mL
anh. sodium sulfate	

Part B

lavender flowers	15 g
dichloromethane	300 mL
anh. sodium sulfate	

Instrumentation and glassware:

round-bottom flask 250 mL
condenser
heating mantle
funnel
separatory funnel 250 mL

steam distillation set (boiler, condenser, flask 500 mL, distillation head, heating mantle, conical flask 2 x 250 mL, plastic joints, rubber pipe)
separatory funnel 250 mL

The main aim of this experiment is isolation of lavender oil form lavender flowers with two methods (Part A and Part B) and in the next step comparison of the yield of these two methods. Linalyl acetate and linalyl butyrate are the main components of lavender oil, which gives lavender flowers their characteristic smell.

Part A

Place 15 g of lavender flowers into a round-bottom flask (250 mL) and pour 100 mL of dichloromethane (add boiling chips!). Heat mixture for 1h then cool down to the room temperature and separate flowers from solution by filtering on a funnel with a paper filter. Concentrate the obtained greenish solution under reduced pressure and weigh.

Thin layer chromatography (TLC):

Use SiO_2, hexane / ethyl acetate (3: 1). Remove the plate and let the solvent evaporate. Once dry, use a hot plate and carefully heat the TLC plate and you will see that the plate is stained by UV light. Mark the spot in pencil. Then, using forceps, dip the plate into a closed jar containing SiO_2 saturated with I_2.

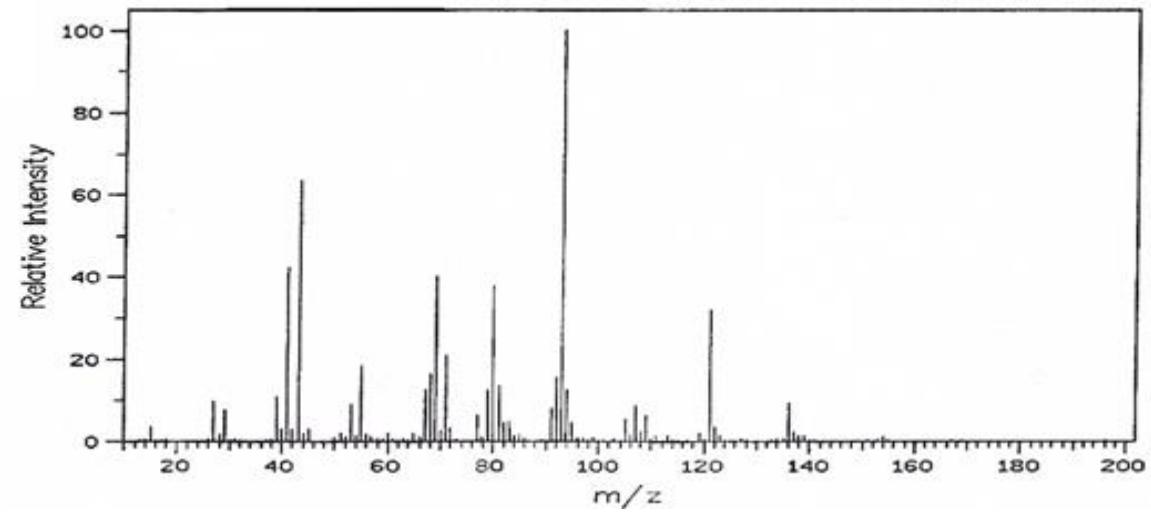
Part B

Figure 6. Steam distillation.

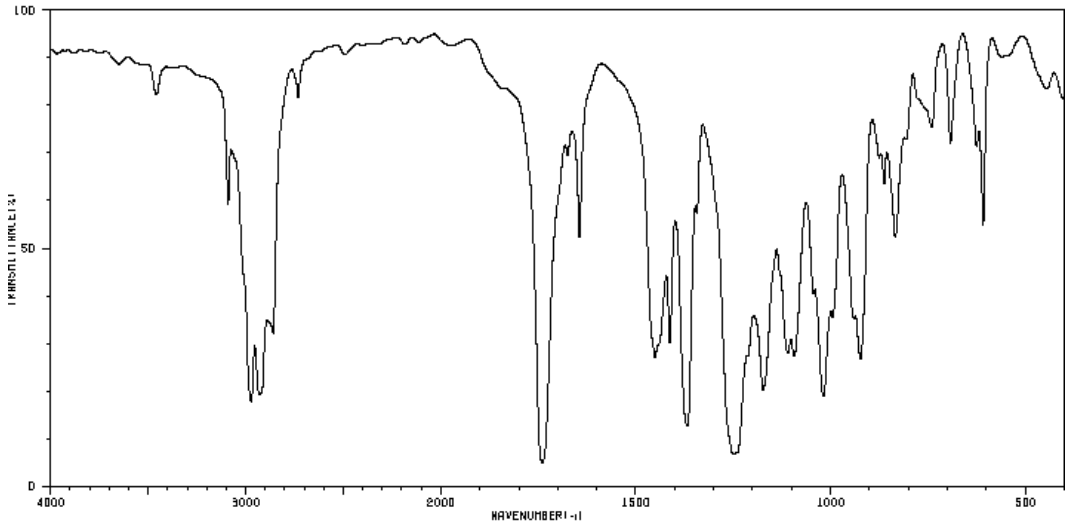
Assemble set for steam distillation (**Fig**. **6**). Place 15 g of lavender flowers into round-bottom flask (500 mL) and add 100 - 150 mL of distilled water. Then, run distillation till 300 mL of distillate is obtained. Next, carry the distillate into separatory funnel and extract efficiently using chloroform or ethyl acetate (5 x 50 mL). Combine obtained extracts and dry them over anhydrous magnesium sulfate. Then concentrate it under reduced pressure. Weigh and calculate the yield of received oil. In a summary compare the amounts, smell and color of obtained lavender oils in method A (two steps) and B. Compare the efficiency and data of both procedures (TLC in part A, FT-IR).

SPECTRA

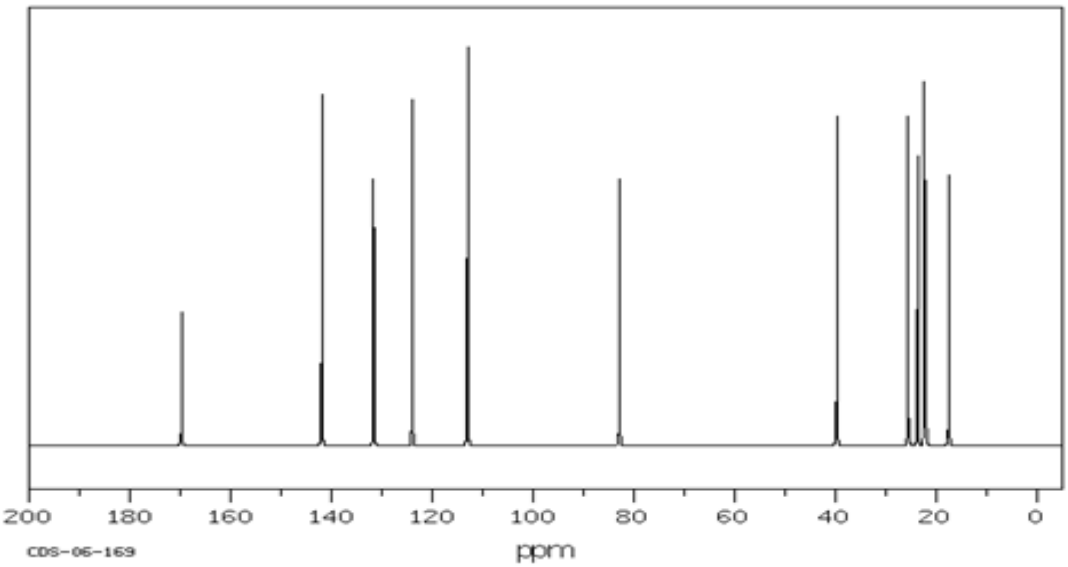
a) EI MS spectrum of linalyl acetate.



b) FT IR spectrum of linalyl acetate.



c) ^{13}C NMR spectrum of linalyl acetate.

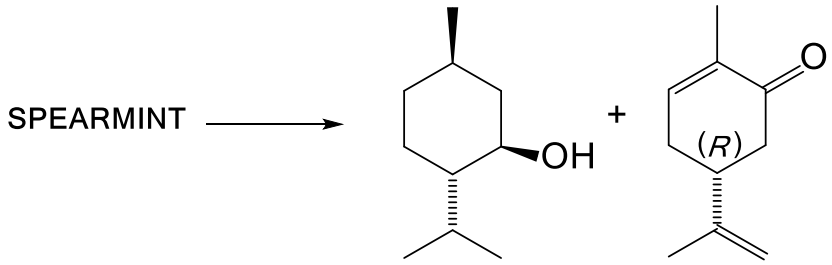


ppm values
169.72
141.93
131.62
123.95
113.01
82.86
39.72
25.63
23.70
22.44
22.09
17.53

References:

http://ochemlabtechniques.blogspot.com/p/how-steam-distillation-works.html

33. MENTHOL AND (R)-(-)-CARVONE



Part A

Reagents:		**Instrumentation and glassware:**
spearmint	20 g	steam distillation system with 500 mL flask
chloroform	60 mL	dropping funnel 250 mL
anh. magnesium sulfate		Separating funnel 500 mL
valine	1 g	Conical flask 250 mL
10% sulfuric acid	100 mL	round-bottomed flask 250 mL
		round-bottomed flask 50 mL

In round-bottomed flask place 20 g of crushed pepper mint and add 150 mL f water. Prepare the set for steam distillation (**Fig**. **6**, chapter 32). Collect ca. 300 mL of the distillate that contains carvone. Extract the product with chloroform (4 x 30 mL) in a separating funnel. Combine the extracts, wash them with distilled water (2x20 mL) and dry above anh. $MgSO_4$.

Filter the dry extract through the glass funnel with a small plug of cotton and transfer the filtrate to a clean 250 mL round-bottomed flask. Concentrate the solution to 15 mL and transfer it by a pipette to a smaller weighted flask (50 mL), evaporate the solvent on an evaporator. The yield 300 mg (R)-(-)- carvone, $[\alpha]^{20}_D = -61^o$ (c=1, EtOH).

Thin layer chromatography (TLC):

on SiO_2, hexane/ethyl acetate (9:1). Remove the plate and allow the solvent to evaporate. After drying, using forceps dip your plate into already prepared reagent: valine 1 g in 100 mL 10% H_2SO_4. After drying use a hot-plate and heat the TLC plate carefully and you will see spots develop on the plate. The spot of carvone turns to pinkish color.

Thin layer chromatography (TLC):

on SiO_2, hexane-methanol-chloroform (8:2:2). Remove the plate and allow the solvent to evaporate. After drying, using forceps dip your plate into already prepared solution of phosphoromolibdenic acid (5 g) in 25 mL of ethanol. After drying use a hot-plate and heat the

TLC plate carefully up to 100 ^{o}C and you will see spots develop on the plate. The spot of menthol turns into blue colour.

Part B

Reagents:

spearmint	20 g
diethyl ether	150 mL
valine	1 g
10% sulfuric acid	100 mL
acetone	

Instrumentation and Glassware:
Conical flask 500 mL
round-bottomed flask 250 mL
round-bottomed flask 50 mL
filtering system with Büchner funnel

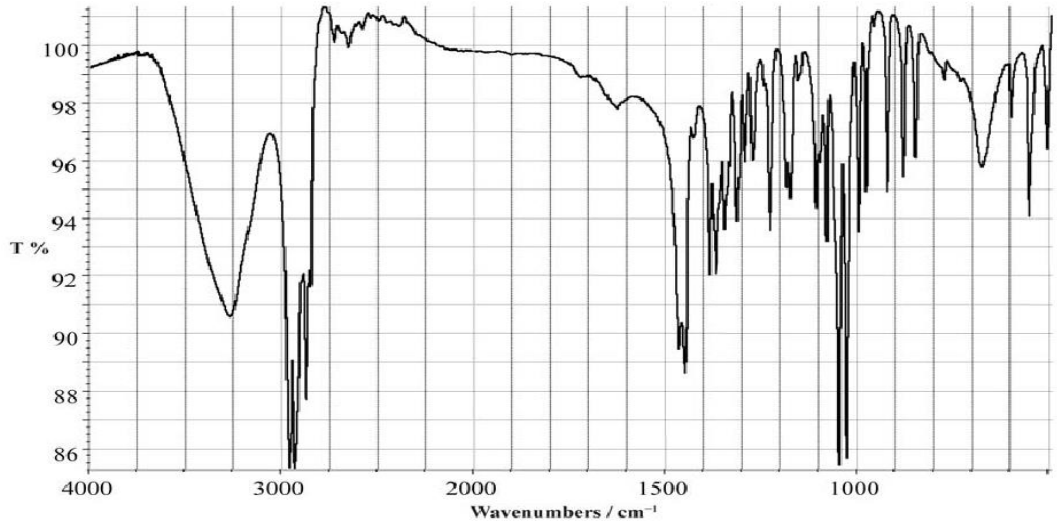
Measure 10 g of crumbled spearmint into a 200 mL conical flask and add 80 mL of diethyl ether. Mix it thoroughly and allow the mixture to stand for 30 minutes. Once the mint has soaked for appropriate time, use the Büchner funnel to filter the mixture (always clamp the filter flask). When you have filtered the solution, wash twice the conical flask with ether (2x10 mL) and wash the mint in the funnel with this solution. After washing the sediment with additional portions of ether, transfer the filtrate to a 250 mL round-bottomed flask. Wash additionally the receiving flask with CH_2Cl_2 and concentrate to 15 mL on an evaporator.
Then move it by a pipette to smaller weighted flask (50 mL) and evaporate the solvent on evaporator. The yield 300 mg (R)-(-)-carvone, $[\alpha]^{20}_{D} = -61^{o}$ (c=1, EtOH).
Calculate the yield in relation to the used spearmint leaves.

Thin layer chromatography (TLC):
on SiO_2, hexane/ethyl acetate (9:1). Remove the plate and allow the solvent to evaporate. After drying, using forceps dip your plate into already prepared reagent: valine 1 g in 100 mL 10% H_2SO_4. After drying use a hot-plate and heat the TLC plate carefully and you will see spots develop on the plate. The spot of carvone turns to pinkish color. The other yellowish and brownish spots come from limonene and leaves pigments (like chlorophylls).

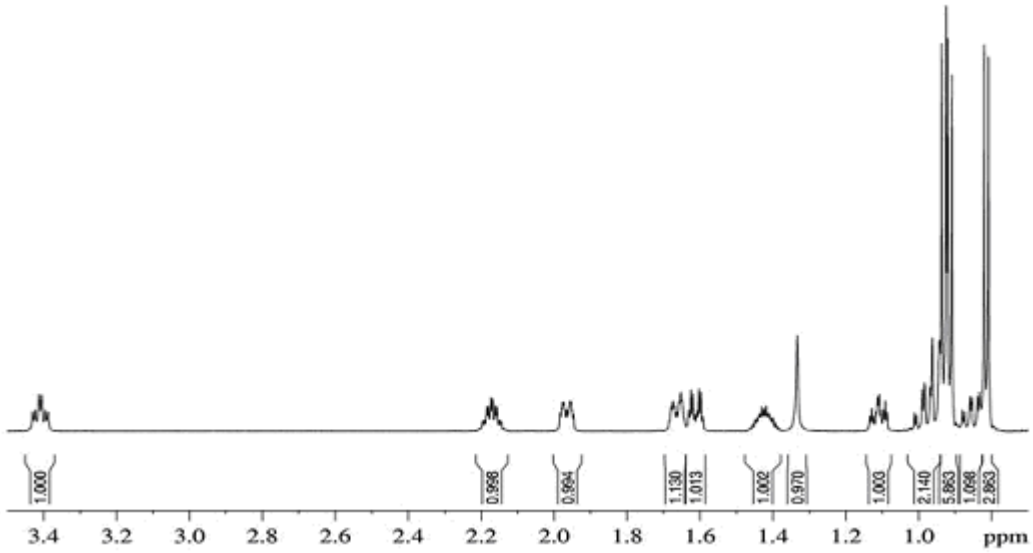
Thin layer chromatography (TLC):
on SiO_2, hexane-methanol-chloroform (8:2:2). Remove the plate and allow the solvent to evaporate. After drying, using forceps dip your plate into already prepared solution of phosphoromolibdenic acid (5 g) in 25 mL of ethanol. After drying use a hot-plate and heat the TLC plate carefully up to 100 ^{o}C and you will see spots develop on the plate. The spot of menthol turns into blue color.

SPECTRA

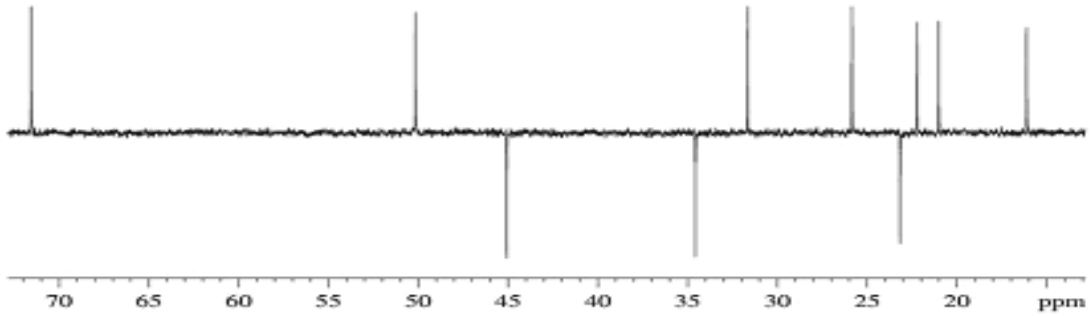
a) FTIR spectrum of menthol in KBr disc.



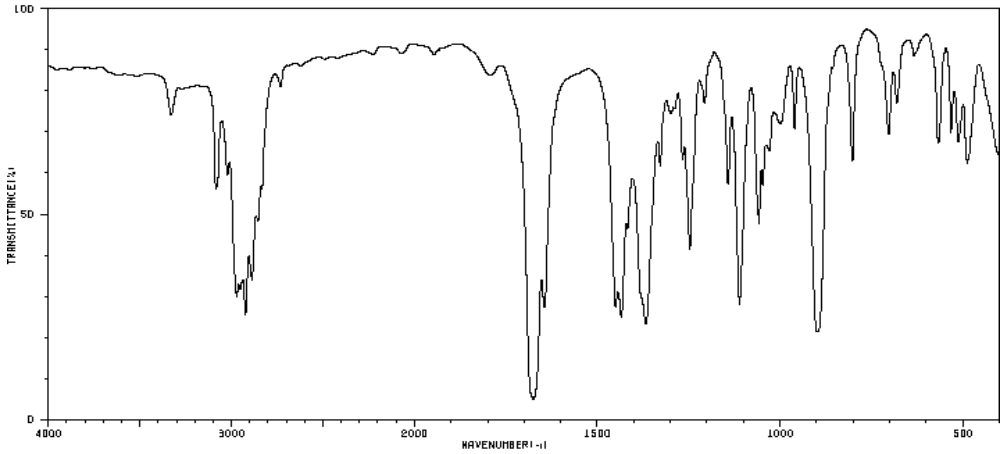
b) ^{1}H NMR spectrum of menthol in $CDCl_3$ (600 MHz).



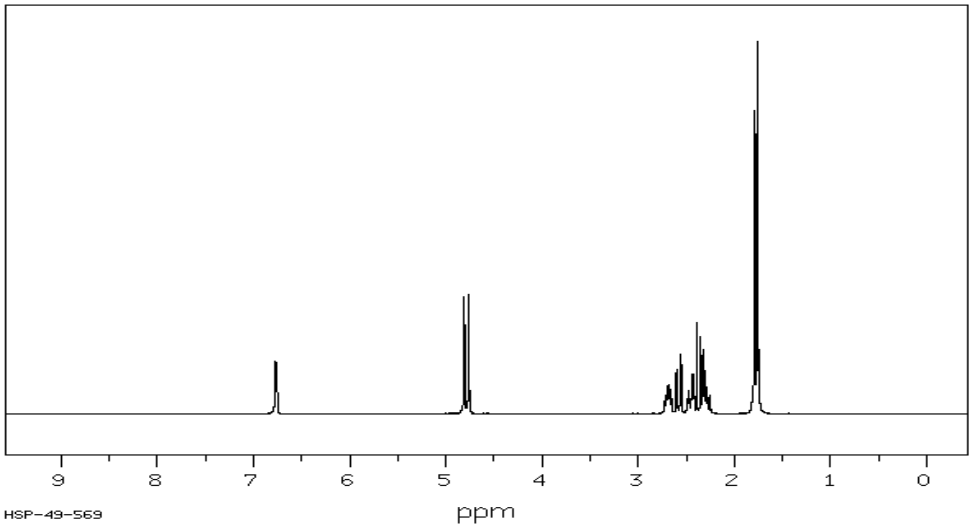
c) APT ^{13}C NMR spectrum of menthol in $CDCl_3$ (150 MHz).



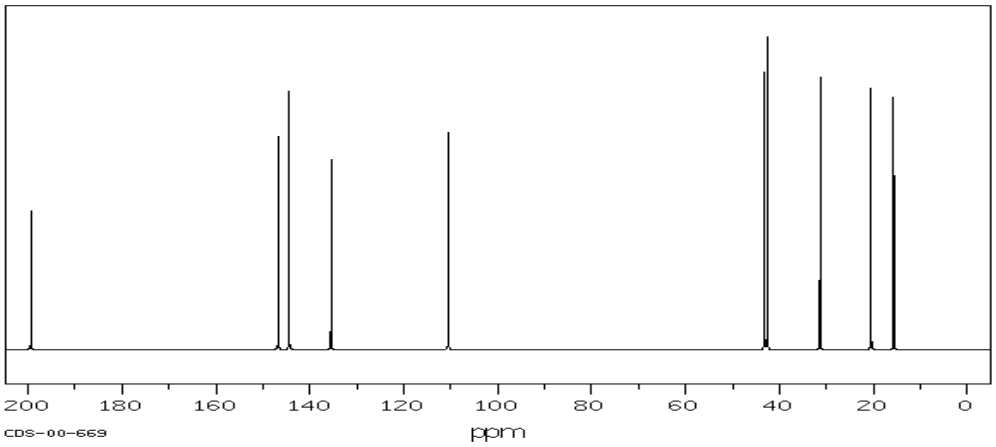
d) FTIR spectrum of carvone, liquid film.



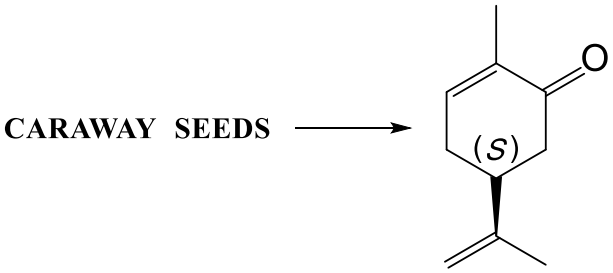
e) ^{1}H NMR spectrum of carvone in $CDCl_3$ (400 Hz)



f) ^{13}C NMR spectrum of carvone in $CDCl_3$.



34. (S)-(+)-CARVONE



Part A

Reagents:		**Instrumentation and Glassware:**
grounded seeds of caraway	20 g	steam distilling system with flask 500 mL
chloroform	60 mL	dropping funnel 250 mL
anh. magnesium sulfate		separating funnel 500 mL
valine	1 g	conical flask 250 mL
10% sulfuric acid	100 mL	round-bottomed flask 250 mL
		round-bottomed flask 50 mL

In round-bottomed flask place 20 g of crushed caraway seeds and add 150 mL f water. Prepare the set for steam distillation (**Fig**. **6**, chapter 32). Collect ca. 300 mL of distillate that contains carvone. Extract the product with chloroform (4 x 30 mL) in separating funnel. Combine the extracts, wash them with distilled water (2x20 mL) and dry above anh. $MgSO_4$.

Filter the dry extract through the glass funnel with small plug of cotton and transfer filtrate to a cleaned 250 mL round-bottomed flask. Concentrate the solution to 15 mL and move it by a pipette to smaller weighted flask (50 mL) and evaporate the solvent on evaporator.

The yield 300 mg (S)-(+)-carvone, $[\alpha]^{20}_D = -61^o$ (c=1, EtOH).

Thin layer chromatography (TLC): on SiO_2, hexane/ethyl acetate (9:1).

Remove the plate and allow the solvent to evaporate. After drying, using forceps dip your plate into already prepared reagent: valine 1 g in 100 mL 10% H_2SO_4. After drying use a hot-plate and heat the TLC plate carefully and you will see spots develop on the plate. The spot of carvone turns to pinkish-orange color.

Part B

Reagents:	
grounded seeds of caraway	20 g
diethyl ether	80 mL
acetone	
valine	1 g
10% sulfuric acid	100 mL

Glassware:
conical flask 200 mL
filtering system with Büchner funnel
round-bottomed flask 250 mL
round-bottomed flask 50 mL

Measure 10 g of crushed caraway seeds into a 200 mL conical flask and add 80 mL of diethyl ether. Mix it thoroughly and allow the mixture to stand for 30 minutes. Once the seeds have soaked for appropriate time, use the Büchner funnel to filter the mixture (always clamp the filter flask). When you have filtered the solution, wash twice the conical flask with ether (2x10 mL) and move it on the seeds in the funnel. After washing the sediment with additional portions of ether, transfer the filtrate to a 250 mL round-bottomed flask. Wash additionally the receiving flask with CH_2Cl_2 and concentrate to 15 mL on evaporator.

Then move it by a pipette to smaller weighted flask (50 mL) and evaporate the solvent on evaporator. The yield 300 mg (S)-(+)-carvone, $[\alpha]^{20}_D = -61^o$ (c=1, EtOH).

Calculate the yield in relation to the used caraway seeds.

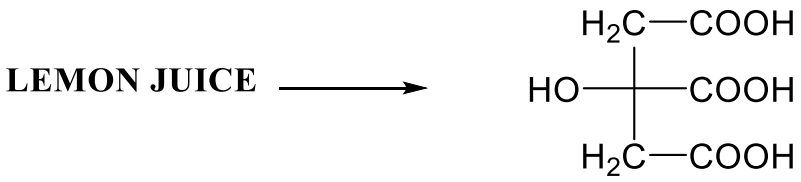
Thin layer chromatography (TLC): on SiO_2, hexane/ethyl acetate (9:1).

Remove the plate and allow the solvent to evaporate. After drying, using forceps dip your plate into already prepared reagent: valine 1 g in 100 mL 10% H_2SO_4. After drying use a hot-plate and heat the TLC plate carefully and you will see spots develop on the plate. The spot of carvone turns to pinkish-orange color. The other yellowish and brownish spots come from limonene and leaves pigments (like chlorophylls).

SPECTRA

FTIR, ^{1}H NMR and ^{13}C NMR **spectra of carvone** are presented in chapter 33.

35. CITRIC ACID



Reagents:		**Glassware:**
Lemon juice	(ca. 100 mL – 3 lemons)	Magnetic stirrer
$CaCl_2$	5 g	beakers 250 mL (3)
10% NaOH		Measuring cylinders (2)
2M H_2SO_4		filtering system with Büchner funnel
2M HCl		flask 100 mL
2M NaOH		Pipettes (2)
		Pasteur's pipettes
		beaker 50 mL
		glass rod

Place a beaker (v. 250 mL) on a stirrer and pour into it 100 mL of fresh squeezed lemon juice (weight it!). Add dropwise slowly and carefully 10% aqueous NaOH basifying the mixture up to pH = 8. You will recognize this moment by changing of the color from light yellow to light orange. Filter the obtained mixture on a Büchner funnel through the "Celite cake". Insert the filter paper and a layer of Celite into the funnel, which must be thoroughly beaten to a thickness of 0.5 cm and put another filter paper on top. Pour the prepared mixture onto the funnel.

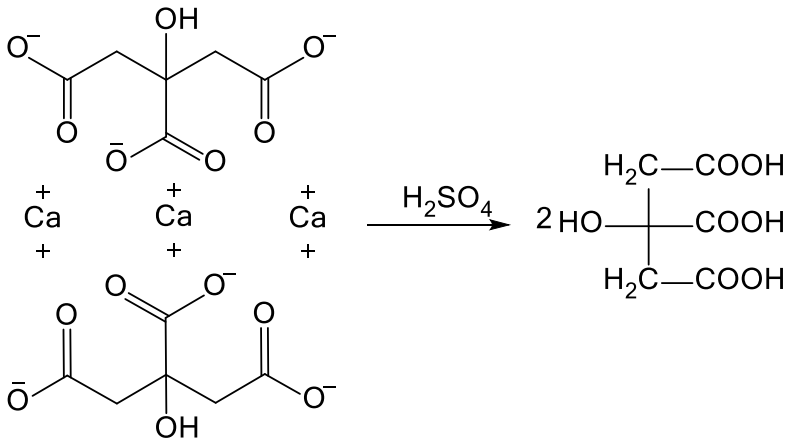
Move the obtained transparent layer to the beaker, place it on a stirrer and add 50 mL of 10% aqueous $CaCl_2$.

Stir for 15 minutes, then heat it to boiling and filter calcium citrate ($Ca_3C_{12}H_{10}O_{14}$) from the hot mixture on a Büchner funnel. Wash the obtained product on funnel with hot water.

Dissolve the obtained crude product in 5 mL of 2M HCl. Then to the solution slowly add 2M NaOH to pH = 7.5 and heat the mixture to boiling. Filter the precipitate on Büchner funnel and air dry.

Weight the product and calculate the yield relative to the amount of the fresh lemon juice.

TRANSFORMATION OF CALCIUM CITRATE TO CITRIC ACID



$$Ca_3C_{12}H_{10}O_{14} + 3H_2SO_4 \longrightarrow 2C_6H_8O_7 + 3CaSO_4$$

To transform calcium salt into citric acid, add to it the proper amount of 2 M aqueous H_2SO_4 (calculate it according to the reaction).

Stir with a glass rod and leave to stand for 10 min. Then filtrate the sediment of $CaSO_4$ on a Büchner funnel with "Celite cake", move to the beaker and concentrate the aqueous layer to 10 mL by boiling on a hot-plate. Cool down concentrated solution and after a few minutes the crystals of citric acid should appear. Filter the product obtained, dry it in the air and weigh. Measure the melting point (152-154 ^oC). Calculate the yield of citric acid relative to lemon juice used.

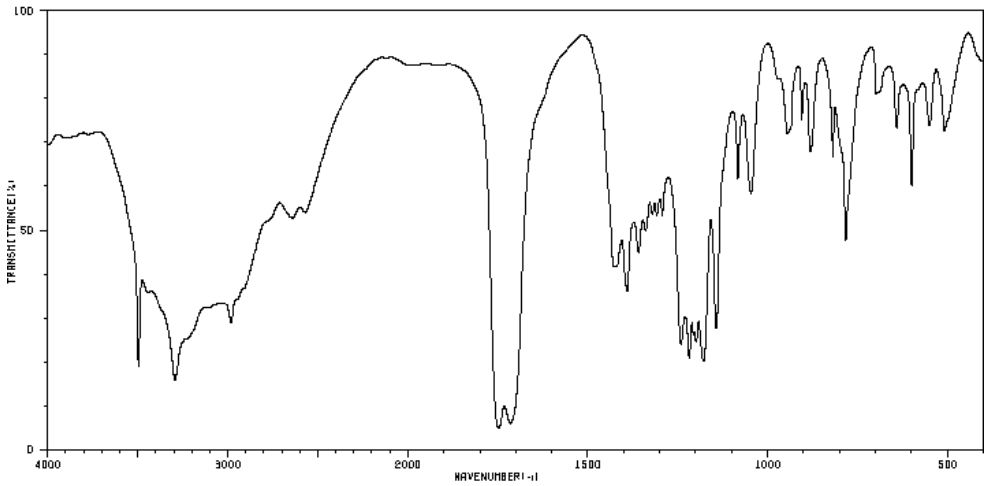
Thin layer chromatography (TLC):

on SiO_2, methanol - aq. ammonia (5:2).

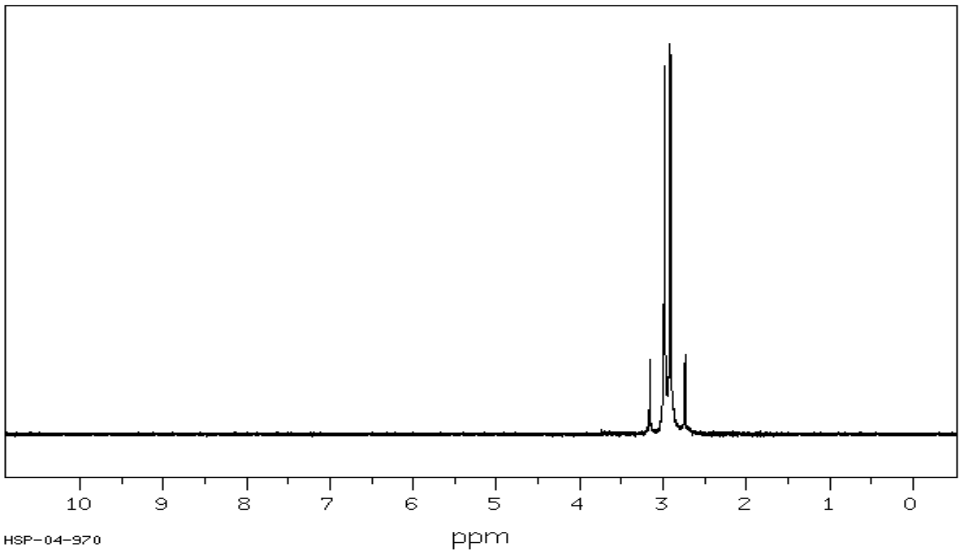
Remove the plate and allow the solvent to evaporate. After drying use a hot-plate and heat the TLC plate carefully and you will see spots develop on the plate.

SPECTRA

a) IR spectrum of citric acid in KBr disc.



b) ^{1}H NMR of citric acid in D_2O (90 MHz).



36. LAURIC ACID FROM COCONUT

Flaked coconut $\longrightarrow$ **coconut oil** with $CH_3(CH_2)_{10}COOH$ **lauric acid - main component**

Reagents:

coconut flakes	2 x 15g
petroleum ether	100 mL
chloroform	250 mL
anhydrous magnesium sulfate	

Instrumentation and glassware:

conical flask 300 mL
Round-bottomed flask 250 mL
reflux condenser
funnel
boiling chips

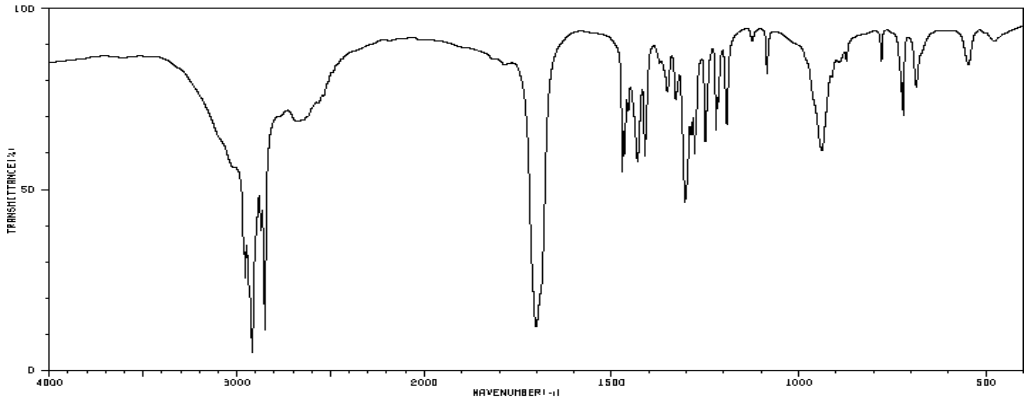
Extraction with petroleum ether. Place 15 g of flaked coconut in round-bottomed flask (250 mL) and add 100 mL of petroleum ether and heat under reflux for 1 hour. Then cool down the mixture and filter coconut flakes from the solution on a funnel with filter paper. Transfer the recovered flakes once more to the round-bottom flask, add petroleum ether and reflux for 1 hour.
Repeat the process one more time, using the same already extracted flakes. Combine obtained 3 extracts and concentrate resulting solution under reduced pressure in flask with known mass. Weigh and calculate the yield of received oil. Coconuts contain ca. 40 % of lauric acid.

Thin layer chromatography (TLC):

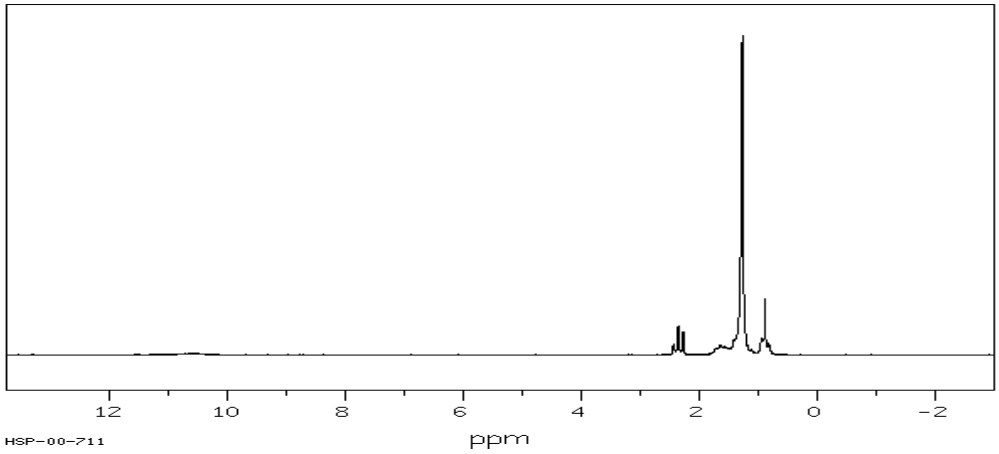
Use SiO_2, $CHCl_3$/MeOH (5:5). Remove the plate and allow the solvent to evaporate.
After drying use a hot-plate and heat the TLC plate carefully and you will see spots develop on the plate.

SPECTRA

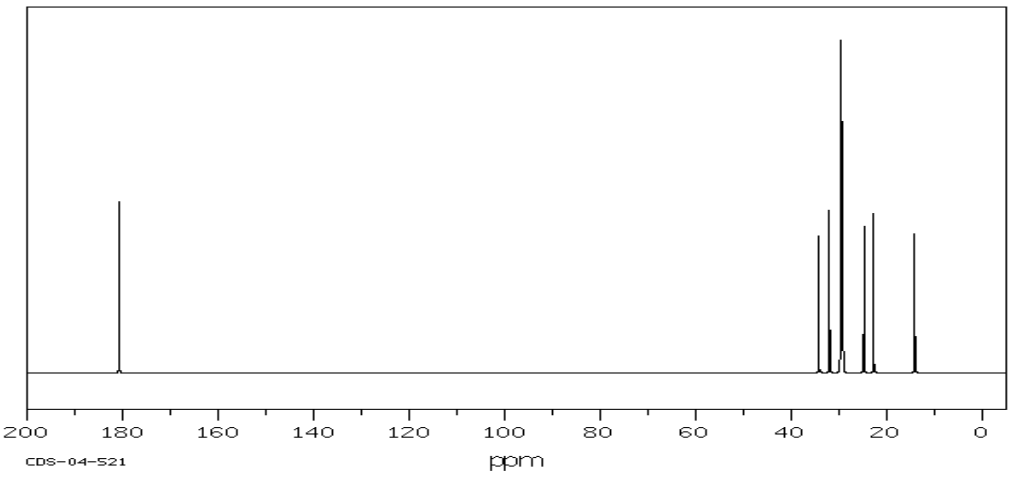
a) FTIR of lauric acid in KBr disc.



b) ^{1}H NMR spectrum of lauric acid in $CDCl_3$ (90 MHz).



c) ^{13}C NMR spectrum of lauric acid in $CDCl_3$ (90 MHz).



References

http://ochemlabtechniques.blogspot.com/p/how-steam-distillation-works.html

37. REFERENCES

Bachmann W. E.: Triphenylchloromethane. *Org. Synth.*, 23, 1943, 100 (DOI: 10.15227/orgsyn.023.0100)

Bansal M., Kaur K., Tomar J., Kaur L.: Synthesis of Flavones. *Biomed J Sci & Tech Res.*, 1 (6) (2017) 1752-1755.

Bari S.S., Bose A. K., Chaudhary A.G., Manhas M. S., Raju V. S., Robb A. W.: Solvent free synthesis of N-Sulfonylimines using microwave Irradiation, *J. Chem. Ed*. 69 (11) (1992) 938

Bhat S.V., Nagsampagi B.A., Sivakumar M., Chemistry of Natural Products, Springer, 2005.

Black C., Buchanan G. L., Jarvie A. W.: A synthesis of (±)-pulegone. *J. Chem. Soc*. 1956, 2971-2972.

Burlingham B. T., Rettig J. C.: Evaluating Mechanisms of Dihydroxylation by Thin-Layer Chromatography. A Microscale Experiment for Organic Chemistry. *J. Chem. Educ*. 85(7) (2008) 959–961.

Caudle R., Siegel G., Wood W. F.: Preparation of Propyl *N,N*-Diethylsuccinimate: An Insect Repellent. *J. Chem. Educ*. 59 (1982) 1069.

Clarke R. J.: The Flavour of Coffee. *Dev. Food Science*. 3B (1986) 1-47.

Corey E. J., Ensley H. E., Suggs J. W.: Convenient synthesis of (S)-(-)-pulegone from (-)-citronellol. *Org. Chem.* 41 (2) (1976) 380-381. doi.org/10.1021/jo00864a047

Corey E.J., Czakó B., Kürti L.: Molecules and Medicine, Wiley, 2007.

Dewick P. M.: Medicinal Natural Producs: a Biosynthetic approach, Wiley, 2nd Ed., 2002.

Gawroński J., Gawrońska K., Kacprzak K., Kwit M.: Współczesna synteza organiczna. Wybór eksperymentów, Wydawnictwo Naukowe PWN, 2012.

González-Calderón D., González-González C. A., Fuentes-Benítes A., González-Romero C.: Synthesis of caffeine from theobromine: bringing back an old experiment in a new setting. *Educ. quím.*, 26 (2015) 9-12.

Jain S., Kumar P., Joshi Ch., Srivastava A.K., Gupta P., Boukherroub R.: Visible Light Assisted Photocatalytic [3+ 2] Azide–Alkyne “Click” Reaction for the Synthesis of 1, 4-Substituted 1, 2, 3-Triazoles Using a Novel Bimetallic Ru–Mn Complex. Supporting information ACS *Sus. Chem. Eng.* 2016, 4 (1), pp 69–75.

Kar A.: Advanced Practical Medicinal Chemistry. New Delhi: New Age International Limited; 2006.

Kshatriya R. B., Shaikh Y. I., Nazeruddin G. M.: Synthesis of Flavone Skeleton by Different Methods. *Orient. J. Chem.*, 29(4) (2013) 1475-1487.

Lucas J. M., Kaneko J. J., Hirohara K., Kleiber M.: Separation of Milk Components, Chromatographic Isolation of Citric Acid and Lactose from Skim Milk. *J. Agric. Food Chem.*, 7 (1959) 638.

Mayo D. W., Pike R. M., Forbes D. C.: Microscale Organic Laboratory: With Multistep and Multiscale Syntheses, 5th Edition, John Wiley & Sons, 2010

Parsons B.A., Dragojlovic V.: Demonstration of a runaway exothermic reaction: Diels-Alder reaction of (*2E*,*4E*)-2,4-hexadien-1-ol and maleic anhydride, *J. Chem. Educ*. 88, 2011, 1553–1557.

Pavia, D. L.; Lampman, G. M.; Kritz, G. S.; Engel, R. G. *Introduction to Laboratory Techniques*, 4th Ed. Thomson Brooks/Cole: Mason, OH, 2006; pp 46-50.

Rigamonti M. G., Gatti F. G.: Stereoselective synthesis of hernandulcin, peroxylippidulcine A, lippidulcines A, B and C and taste evaluation. *Beilstein J. Org. Chem.* 11 (2015) 2117–2124. doi:10.3762/bjoc.11.228

Sharpless W.D., Wu P., Hansen T.V., Lindberg J.G.: Just Click It: Undergraduate Procedures for the Copper(I)-Catalyzed Formation of 1,2,3-Triazoles from Azides and Terminal Acetylenes. *J. Chem. Educ.* 82 (2005) 1833–1836.

Surya Prakash Rao H., Kamalraj M., Prabakaran M.: Synthesis and physico-chemical properties of H-cardanol triazole zinc porphyrin conjugate. *RSC Advances* 9 (2019) 4499-4506/ Supporting information. doi: 10.1039/C8RA09998G.

Svirbely W. J., Eareckson W. M., Matsuda K., Pickard H. B., Solet J. S., Tuemmler W. B.: Physical Properties of Some Organic Insect Repellents. *J. Am. Chem. Soc.* 71 (1949) 507.

Vogel A.I., Furniss B.S., Hannaford A.J., Smith P.W.G., Tatchell A.R., *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Prentice Hall, 1996.

Wohlk, *Zeitschr. F. Anal. Ch*. (1904), 670. „Odczynnik na cukier mleczny i maltozę”

Chemik Polski, nr 21, 24 (11) maja 1905r (V), 408.

Zhuang C., Zhang W., Sheng C., Zhang W., Xing C., Miao Z. **:** Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem. Rev. 117 (12)* **(**2017) 7762-7810.

https://open.bu.edu/handle/2144/1494

https://pdfs.semanticscholar.org/8065/5d9b7f48e1b55f34ae6bf58b285079f778a8.pdf

https://instruct.uwo.ca/chemistry/283g/labs/Experiment%202/Spectral%20Data%20Exp%202%20_2007.pdf

https://www.slideshare.net/AbarnaAbi1/soxhlet-apparatus
http://www.coffeeresearch.org/science/sourmain.htm
http://www.chemistry.mcmaster.ca/~chem2ob3/nhw_temp/old_old_labmanual/expt5/2ob3exp5.html
http://ochemlabtechniques.blogspot.com/p/how-steam-distillation-works.html

SPECTRA

SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology, 2018.07.18)
http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, date of access) (SDBS No.:2569)
https://archives.library.illinois.edu/erec/University%20Archives/1505050/chem337/onlinesyllabus/onlinesyllabus/chem337Expt10B_rxn_anthracene.html
https://www.chegg.com/homework-help/consider-spectral-data-9-fluorenol-figs-1713-1714-function-chapter-17.4-problem-14e-solution-9781439049143-exc
https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-228-S1.pdf
www.chemicalbook.com/SpectrumEN_108-31-6_1HNMR.htm
https://sdbs.db.aist.go.jp/sdbs/
http://webbook.nist.gov/cgi/cbook.cgi?ID=C96612214&Mask=80
http://www.sigmaaldrich.com
https://www.guidechem.com/
https://spectrabase.com/
https://www.ebiochemicals.com/Wiki/QcEB000031998_HNMR_1.html
https://www.chemicalbook.com/SpectrumEN_141-95-7_13CNMR.htm
https://orgspectroscopyint.blogspot.com/2014/11/citronellolcosy.html
https://orgspectroscopyint.blogspot.com/2016/03/citronellal.html
https://www.chegg.com/homework-help/questions-and-answers/interpret-1-h-13c-nmr-spectra-benzil--label-different-types-protons-carbons-com.p.ound-locat-q27496581
https://spectrabase.com/spectrum/C1TK3Ezcc3H?a=SPECTRUM_C1TK3Ezcc3H
https://pubchem.ncbi.nlm.nih.gov/com.p.ound/Anthracene-maleic-anhydride-diels-alder-adduct#section=Mass-Spectrometry&fullscreen=true